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THE MEDICAL CLINICS
OF
NORTH AMERICA

Volume 10 No. 1

CLINIC OF DR. THOMAS McCRAE

JEFFERSON HOSPITAL

CARCINOMA OF THE BRONCHUS: HEMIPLEGIA. A DIAGNOSTIC STUDY

THE problem of diagnosis is presented to us in very different ways. In some cases there seems no doubt of the answer, as, for example, in an ordinary case of lobar pneumonia; in that the greatest difficulty may be to recognize a complication, such as empyema. In other cases it may be impossible for a time to come to any conclusion or even suggest a tentative diagnosis with any degree of certainty. In other cases it may represent a balance of probabilities without any positive evidence either way. It is in these cases that particular interest lies, and this patient is an example. You will have to put your wits to work to solve this problem, which is a difficult one. There is a great intellectual interest in such an exercise, and anything which sets us thinking is educational. Mr. A., will you give us the history of the patient?

MR. A.: The patient is a white female, aged thirty-seven, who comes complaining of loss of power in the right arm and right leg, shortness of breath and cough, and nausea and vomiting. She was admitted on January 5, 1926.

DR. McCRAE: What impresses you in the complaints?

STUDENT: There are two different sets of symptoms, or perhaps three. There is the hemiplegia, which means a lesion in the nervous system, with other complaints suggesting thoracic disease and possibly gastric disease.

Family History.—This is negative. There is no history of tuberculosis or new growth.

Past History.—Measles and mumps are the only infectious diseases she has had. There is no history of pneumonia, pleurisy, tonsillitis, or influenza, and she has not been subject to colds. There is no history of gastro-intestinal disease. She has not had any operations or injuries. She has been married for ten years and has one child living and well; her first child died two weeks after birth from malnutrition. She has not had any miscarriages. She has always regarded herself as very healthy.

Present Illness.—Late in October, 1925 she had a "cold in her chest" accompanied by cough, but there was no fever and she did not go to bed. The cough was productive, the sputum being white and frothy, but it did not contain any blood. At the end of a week the cough ceased, but she did not feel any better. Soon after this she had pain in the lower right chest posteriorly and felt weak and tired. She was then told that she had pleurisy and, a week later, that she had pus in her chest. This was about the middle of November. The right side was tapped and 2 quarts of fluid were removed, which was clear and looked like urine. A few days later she became dyspneic and had a heavy feeling in the chest. She was tapped a second time early in December, with the same result as before. She has been up and about all this time, but felt very weak and has had a great deal of shortness of breath. There has been no cough except at the onset, no night-sweats, and no hemoptysis. She does not know whether she has had fever.

DR. McCRAE: What does this part of the history suggest?

STUDENT: Pleurisy with effusion.

DR. McCRAE: Have you any suggestion as to the cause merely on general principles?

STUDENT: The chances are that it is tuberculous.

DR. McCRAE: That is correct. Now let us have the other side of the story.

MR. A: About the middle of November, 1925 she noticed that the fingers of her right hand were shaky and that she could not write. The following day on getting up in the morning she

found that she could not use her right arm. There was some twitching occasionally and tingling in the arm at first, but this did not last long. She does not think there was disturbance of sensation and there was no pain. The paralysis of the right arm has continued until the present time.

About the middle of December, 1925 she began to notice weakness of the right foot and the calf of the leg felt very heavy. This weakness gradually increased, and at the present time she drags the right leg and can only step on the ball of the foot. She has not noted any change in sensation. She has not had any double vision during this period, and there has not been any muscular twitching of any other part of the body except the right arm.

She has had a great deal of nausea, accompanied by occasional vomiting. Since her present illness she has been very constipated. No blood has been passed in the stools. She has lost a good deal of weight, probably between 15 and 20 pounds.

DR. MCCRAE: What possibilities have occurred to you as an explanation of this combination of symptoms?

STUDENT: There may be two entirely separate diseases or the two conditions may be associated.

DR. MCCRAE: In case of the latter, what suggestions do you offer?

STUDENT: First, that both are due to tuberculosis; second, that there is a neoplasm with metastasis to the brain.

DR. MCCRAE: Are there any other possibilities? Mr. A. has given us the most common ones, but in such a case as this we have to consider unusual ones. It is well to have as many possibilities in mind as we can from the history before we study the patient. Let us consider what other conditions may be responsible for the hemiplegia.

STUDENT: Intracranial hemorrhage and syphilis.

DR. MCCRAE: Anything else?

STUDENT: The possibility of new growth and tuberculosis has been mentioned.

DR. MCCRAE: Intracranial abscess and actinomycosis should be kept in mind.

STUDENT: Possibly epidemic encephalitis should be considered.

DR. McCRAE: With this disease fairly common, as at present, you do well to suggest this.

Examination.—The patient is thin and anemic looking, somewhat emaciated, and shows slight cyanosis and dyspnea. There is marked dilatation of the veins of the neck, more on the right than on the left side. The thorax shows much less expansion on the right side, with absence of vocal fremitus, flatness, and absence of breath and voice sounds, except at the apex, where there is tympany. There is a paravertebral triangle of dulness at the left base. The heart is displaced to the left, but otherwise shows nothing abnormal. The abdomen is negative.

DR. McCRAE: What do these signs suggest?

STUDENT: Fluid in the pleural cavity.

The thorax was tapped and 1500 c.c. of fluid removed. At first the color was that of a dark serous fluid, but later it was distinctly bloody.

As regards the changes due to the lesion in the nervous system, there is some weakness of the right side of the face, with complete paralysis of the right arm and partial paralysis of the right leg. There is a painful area along the inner border of the right forearm. There is no loss of sensation. The arm reflexes are considerably increased on the right side and normal on the left. The knee-jerk and tendo achillis reflex are more active on the right side than the left. There is no response on trying the plantar reflex on the right side; it is normal on the left; there is no clonus. It is interesting to note that on trying the plantar reflex on the right side, while there is no movement of the right great toe, there is definite crossing of the reflex to the left side.

Remarks.—There is room for considerable speculation as regards the explanation of the lesions in the nervous system. A vascular lesion does not seem very probable. There is no evidence of endocarditis, which might be responsible for embolism, and hemorrhage does not seem likely. The gradual onset and slow progress are against embolism and hemorrhage. Her arteries are soft and the blood-pressure is low. The systolic pressure varies between 100 and 110 and the diastolic remains about

80. The possibility of thrombosis cannot be excluded, but there is no favoring condition present so far as we know. There is no marked anemia; the hemoglobin is 80 per cent., the red cells 4,400,000, and the leukocytes 8000. The urine shows nothing of importance. The Wassermann reaction in the blood and spinal fluid is negative. The study of the spinal fluid gives practically normal results; the fluid is clear, contains 2 cells to the cubic millimeter, reduces Fehling's solution, and does not show any increase in globulin. The possibility of a cerebral vascular lesion or cerebrospinal syphilis seems pretty well ruled out. The possibility of *epidemic encephalitis* was mentioned. This would represent an unusual picture for that disease, but there is one finding which has to be mentioned. The sugar content in the spinal fluid is high. In one specimen it was 0.09 per cent. and in another 0.08 per cent.

This brings us to a consideration of the two conditions mentioned before, namely, tuberculosis and neoplasm.

Tuberculosis.—The occurrence of a pleural effusion is always suggestive of a tuberculous process unless we have evidence suggesting something else. The *fluid* on the first tapping in the hospital contained some blood; on the second tapping it was bloody throughout. This is possible with tuberculosis, but, on the whole, is more suggestive of malignant disease. You will find that the statements in the literature do not agree on this point. The cell count shows a considerable number of lymphocytes, but there are also some large cells with curious nuclei. These cannot be identified positively as proof of malignancy, but are suggestive of it. A guinea-pig has been inoculated, but this does not help us at present.

We have not found any positive sign of tuberculosis elsewhere and it has not been possible to obtain any sputum to examine. The *x*-ray study of the chest shows increase in the peribronchial shadows of the left lung, but this cannot be regarded as due to tuberculosis. As regards the cerebral lesion, there is nothing to suggest a tuberculous meningitis and the study of the spinal fluid on several tappings is against it. The possibility of a tuberculoma cannot, of course, be excluded.

New Growth.—This has to be seriously considered. The bloody pleural fluid and the rapid downward course are in favor of it. The peculiar cells in the pleural fluid may be regarded as suspicious. As regards the intracranial condition, we have no signs which are definite. The examination of the eye-grounds is absolutely negative and the *x*-ray study of the skull is the same. There is no evidence of a metastasis to the bones of the skull. If the intracranial condition is independent of the disease in the thorax, we have little guide as to its nature. A syphilitic process is excluded by all the evidence.

The weight of evidence, and this each must judge for himself, seems to be in favor of malignant disease of the lung, and, if this be accepted, that the intracranial lesion represents a metastasis, but the evidence of intracranial new growth is by no means conclusive, although strongly suggestive.

Course.—The patient's condition steadily grew worse. For about ten days there was slight fever, rarely above 100° F. Then the fever was higher, on one occasion reaching 107° F. The fluid in the pleura did not accumulate to any extent after the second tapping. The paralysis of the right side of the face became more marked and in the few days before death she lost the power of speech. Death came on January 25th, after a total duration of illness of about three months. The impression was that death resulted from the lesion in the nervous system rather than from the thoracic disease.

Remarks.—There is no agreement as to what diagnosis should be made. Those who have studied the patient are divided as is the opinion of the class. The majority favor malignant disease of the lung as the primary lesion with metastasis to the brain. A number feel that tuberculosis is the more probable diagnosis. In view of the possibility of a new growth in the lung you may ask why bronchoscopy was not done. This was considered, but the patient's condition was such that we did not feel that it was justifiable. I do not believe that Dr. Jackson would have been willing to do it in this patient unless there was a fairly reasonable chance that she might be helped, and there was no reason to expect this. The presence of the pleural effusion might be regarded

as a contraindication. How much it might add to the difficulty of bronchoscopy I do not know, but probably not very much.

AUTOPSY (DR. KONZELMAN)

Thorax.—The right pleural cavity is partly obliterated by dense adhesions. The fluid is contained in a cavity which measures about 6 cm. in depth, that is, the distance between the chest

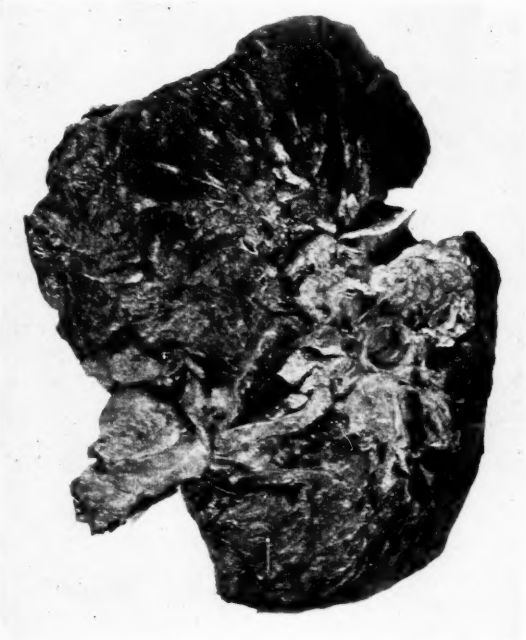

Fig. 1.—Lung with tumor in wall of bronchus and extension into parenchyma.

wall and the lung. The fluid is of the same character as that previously aspirated. The adhesions are particularly dense between the visceral and diaphragmatic pleura.

Lung.—The right lung is collapsed and is covered by thick pleura which has a ragged appearance. About the main bronchus there is a dense mass which is not definitely circumscribed, but

fades into the lung tissue. The area of thickened pleura between the lung and diaphragm shows infiltration. The mediastinal lymph-nodes are enlarged, hard, and show infiltration. There is no evidence of a tuberculous lesion in either lung.

On section of the right bronchus the lumen is found to be narrowed by a dense mass, pearly white in color, which, on section, is hard. There is no dilatation of the bronchus. This mass has invaded the lung tissue adjoining it (Fig. 1).

DR. MCCRAE: What do these findings suggest?

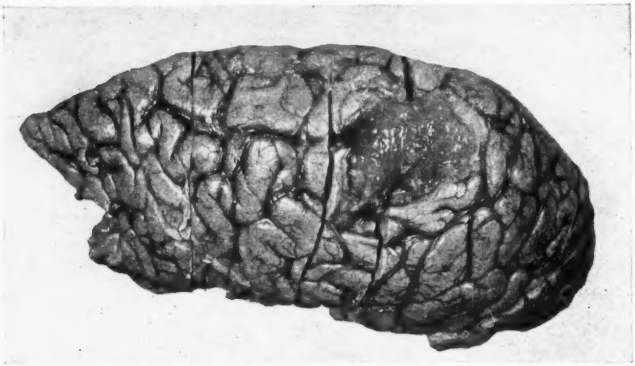

Fig. 2.—Left hemisphere showing gelatinous mass in parietal and frontal region. Gelatinous material has fallen out from the defect in the frontal region.

STUDENT: A new growth of the right bronchus with extension into the right lung and metastasis to the pleura and mediastinal glands.

DR. MCCRAE: It may be that the process has involved the pleura by extension as it has the lung. The process in the diaphragmatic pleura may be a metastasis.

Further study showed that on the upper part of the right lobe of the *liver* there were two elevated and infiltrated nodules. Other nodules were found in the interior of the liver. The mesenteric lymph-nodes, one ovary, and the adrenal glands are also the seat of metastases.

Brain.—This shows a very remarkable condition. In the

left frontal region there is an area about 4 cm. in diameter, amber colored, and composed of curious gelatinous-like material which completely replaces the brain tissue. It is sharply limited with a border which is somewhat irregular, and looks like a bag of jelly which has been inserted in the substance of the brain. The material is soft and shows a tendency to ooze from the surface. In the left parietal lobe is another area of the same character and about the same size. The surrounding brain tissue looks normal and otherwise no gross pathologic lesion is visible (Fig. 2).

DR. MCCRAE: What is your diagnosis of these central lesions?

STUDENT: I do not know.

DR. MCCRAE: I am in the same condition of ignorance, and as the pathologists hesitate to express an opinion we must wait until the brain is hardened and sectioned. We should know more then. The lesions probably extend for some depth, and it is only speculation to try and decide from the surface appearance what they are. You will probably agree with me that it is rather a comfort to find that even with the brain exposed a positive diagnosis is not possible. We have some excuse for not being sure of the nature of the lesion when the skull was between it and us. The gross appearance rather suggests that there may have been cyst formation with degeneration of the contents.

At a subsequent clinic Professor Crowell discussed the pathologic findings.

PROFESSOR CROWELL: The case is one of carcinoma that apparently originated in the wall of the right main bronchus, the lumen of which it largely occluded, without causing ulceration of its mucosa. The wall of the bronchus at this point is much thickened by the presence of the tumor and the tumor extends along the bronchi peripherally into the lung. Grossly this is a firm, white tumor mass giving no suggestion of a gelatinous character. Similar tumor involvement, obviously metastatic, has occurred in the left lung, pleura, liver, adrenals, mediastinal and abdominal aortic lymph-nodes. In all of these places the tumor is of firm homogeneous consistence. In marked contrast

to this condition are the areas of involvement in the brain. Here large cysts have formed beneath the pia-arachnoid, which are filled with a thin gelatinous mass, and which, when support of surrounding structures is removed, hang out like bags of soft jelly. Within the cerebral substance the tumor has a firmer consistence and hemorrhage into it has taken place (Fig. 3).

Microscopically, it was a surprise to find that the tumor of the bronchus and all of its metastases were of the nature of a gelatinous or mucoid carcinoma made up of spaces lined by high epithelium and filled with mucus. Many of the epithelial cells

A B

Fig. 3.—A, Section of tumor in parietal region. B. Same tumor further posteriorly. As indicated by incisions in Fig. 2.

are represented only by nuclear remains in a mass of mucus. Other epithelial cells contain varying amounts of mucus. The stroma is abundant, which accounts for the firm appearance of the tumor as noted grossly.

The *cerebral metastases*, which differ so markedly in gross appearance from the original tumor and its other visceral metastases, differ microscopically only in the greater amount of mucoid substance produced and in the lesser amount of stroma. In the brain the tumor has a more obvious papillary structure than elsewhere.

Similar gelatinous carcinomas in the lung have been described

and their origin has been ascribed to the alveolar epithelium. Without entering into a general discussion of this subject it seems obvious that in this case the origin is in the mucous glands of the mucous membrane of a large bronchus.

In our experience this type of tumor of the bronchus is much less frequent than a solid carcinoma made up of cells that are partly columnar and partly of a flattened squamous character, the difference in character of which may be explained on the basis of metaplasia.

DR. MCCRAE: It has been said that "it is easy to be *wise* after the event, but difficult to be *wiser*." The explanation for the curious appearance of the metastases in the brain is now very evident. If we had done a little harder thinking some of us might have suggested the possibility that the curious gelatinous material was due to metastasis from a new growth originating in the mucous glands of the bronchus. We should know better next time.

Primary Carcinoma of the Lung.—It is worth noting that what is usually described as primary carcinoma of the lung is really *secondary* in the lung tissue proper with the *primary growth* in a bronchus. This may seem a distinction without a difference, but it may have very real importance in one regard, namely, early diagnosis. I venture to say that the vast majority of us, unless we have had occasion to study the point, think of so-called primary carcinoma of the lung as having originated in lung tissue proper. It is situated there after the lung is invaded by extension or metastasis, but we forget that the growth originates in a bronchus in the great majority of cases. Bronchoscopy gives us a means of certain diagnosis of bronchial new growth in some cases, but it is not going to be used if we think of "primary carcinoma of the lung" as always originating in the lung tissue itself. Early diagnosis of a bronchial new growth offers some chance of treatment. Some of you have seen the patient reported by Jackson *et al.*,[1] in whose case, as a result of diagnosis by bronchoscopy, the immediate result was so brilliant. If we will pay more attention to the bronchi in these cases something may be accomplished.

[1] Jour. Amer. Med. Assoc., 1925, 84, 97.

There are some phases of the subject which are worthy of special discussion.

Frequency and Supposed Increase of Primary Cancer of the Bronchi and Lungs.—We must recognize that the disease is not rare and there is considerable evidence to suggest that it is on the increase, especially in the last twenty years. You will find an excellent discussion of the whole question and a large number of statistics quoted in an article by Grove and Kramer.[1] They suggest an incidence of 0.15 per cent. or more of all autopsies, and about 1 per cent. of all carcinoma for primary carcinoma of the lung.

With reference to the increase in its occurrence there are many suggestions as to possible etiologic factors. Influenza is, of course, suggested, as in many other diseases, but the evidence seems very scanty. The suggestion that it is a result of gassing in war has little support. A result of the increased use of *x*-rays in the diagnosis of thoracic disease has been given as an explanation. Some attribute the increase to cigarette smoking. If there is anything in this we should see a continued increase, but the evidence seems hardly worthy of belief. Irritation of the bronchi is naturally suggested, as this is a factor in the production of some carcinomas. That dust and smoke may play a part is a tempting suggestion, but apparently there is no association between pneumoconiosis and carcinoma shown in autopsy reports. Much more weight should be given to the suggestion that irritating substances of a chemical nature may play a part. You are aware that there is a group of new growths produced by chronic contact with tar products. It has been suggested that the inhalation of particles of tar and oil from roads may play a part in the etiology. In addition, the oxidation products of gasoline may have a similar influence. These suggestions are certainly worthy of careful consideration.

Pathology.—There are several possible points of origin of primary carcinoma of the lung: (1) It may arise in the epithelium of the bronchi, and, apparently, as in this case, it usually starts in the large bronchi and not often in the bronchioles. It tends

[1] Amer. Jour. Med. Sci., 1926, 171, 250.

to invade the lung along the bronchi from above downward. The cells may be either cylindric or squamous. In case of the former, cysts may be found containing mucus.

(2) It may arise in the peribronchial glands. This tends to invade the submucosa of the bronchi and also the lymph-spaces in the adjoining lung tissue.

(3) It may arise in the pulmonary epithelium. In one sense we may say that this is really the only true form which can be regarded as absolutely primary carcinoma of the lung tissue.

Some writers have pointed out that it may be very difficult to reach an opinion as to the exact histology of the cells, as inflammatory processes are common, and these may alter the appearance.

Ewing discusses these tumors under three headings, namely, those arising from (*a*) bronchial epithelium, (*b*) alveolar epithelium, and (*c*) bronchial mucous glands. Emphasis is laid on the fact that specific features belong particularly to the early stages. The general opinion is that the majority of these tumors arise from the bronchial epithelium and only a few from the alveolar epithelium. Tumors arising from the mucous glands seem to have quite characteristic features very frequently. Alteration of the mucosa is unlikely, the bronchi are usually narrowed, and the secretion of mucus is a prominent finding.

As a rule, *metastases* are common. In 374 cases reported by Adler metastases were present in all but 33 cases. As one would expect, the lymph-nodes furnish a larger number than the liver (117 and 103 cases in Adler's series). The pleura is not involved as often as might be expected. In Adler's series of 374 cases, in 53 there were metastases to the brain and in 52 to the pleura.

There is much discussion as to the association of carcinoma with tuberculosis. As you know, there is an old statement that patients with tuberculosis very rarely have carcinoma, and there is really a good deal of evidence to support the correctness of this opinion. Some have laid a great deal of stress on tuberculosis in the etiology of carcinoma of the lung, thinking that tuberculosis was an important factor. Studies of the literature do not seem to suggest this.

Clinical Features.—When the possible variations with regard to extent, situation, metastases, etc., are considered, it is evident that it is difficult to describe any very comprehensive clinical picture. For example, the occurrence of fluid in the pleura would alter the symptoms and signs markedly. Of the general features, weakness and loss of weight are usually quite marked. The occurrence of fever is by no means constant, and some writers have emphasized the importance of absence of fever, particularly in the diagnosis between tuberculosis and new growth.

Pain is an exceedingly common complaint, which may be present early. It may vary a good deal in character and sometimes shows radiation. Here again certain writers have laid great stress on its occurrence as important evidence against tuberculosis. Cough and dyspnea will probably vary a good deal. The latter will be influenced considerably by the presence of pleural effusion, and the possibility of pressure from involvement of the mediastinal glands. The frequency of hemoptysis seems uncertain, but it is common enough to be kept in mind as a cause of bleeding in cases of obscure causation.

The physical signs will evidently vary tremendously with the situation and extent of involvement. In some cases the growth may cause practically complete obstruction of the bronchus or may cause partial obstruction, exactly as a foreign body might. Evidently the extent of involvement of the lung tissue will alter the signs very materially. The occurrence of pleural effusion conceals any changes in the lung behind the fluid. As was said before, there is some difference of opinion as to the significance of blood-stained pleural fluid. Some believe that it is just as significant of tuberculosis as of malignant disease. In the present case we found a predominance of lymphocytes. The unusual cells which we found were not definitely recognized as carcinomatous cells, but there is no doubt that the pleural fluid in a suspected case should be very carefully studied with this possibility in mind.

One interesting point brought out by Grove and Kramer is with reference to the blood-pressure. They point out that hypotension is common in tuberculosis. In their series of 21 cases of

primary carcinoma of the lung there was 1 patient in whom the systolic pressure was recorded as below 100. In the patient whom we have studied the blood-pressure on admission was 110 systolic and 76 diastolic. Subsequently the systolic pressure varied between 90 and 100, and in the majority of observations was below 100; the diastolic on one occasion fell as low as 64; it was usually about 80.

In conclusion, emphasis should be placed on the relative frequency of primary carcinoma of the lung (more properly bronchus). It should be given a more important place in the differential diagnosis of obscure lung conditions. In my personal experience the difficulty in diagnosis from tuberculosis has been rather striking, and we have had several patients with new growth referred with this diagnosis. If the signs in the lungs are marked, as they were in these patients, the absence of tubercle bacilli in the sputum is important evidence against tuberculosis. The *x*-ray study is of great aid in the absence of pleural effusion. We would all agree that in the present problem the occurrence of pleural effusion added greatly to the complexity of the problem. Without it the diagnosis should have presented little difficulty.

Lastly, as the great majority of the cases termed "primary carcinoma of the lung" have origin in a bronchus, we may expect to have increasingly greater help from bronchoscopy. Just as in the early diagnosis of carcinoma of the esophagus, a direct inspection of the area involved, with the removal of a portion of tissue for section, gives definite information to be obtained in no other way. This offers great possibilities.

As to **treatment,** not much can be said. The use of *x*-rays is of the greatest value in some cases, but must be palliative only in the majority. It does not seem too much to expect that, with the development of thoracic surgery, we may hope in case of early diagnosis of carcinoma of a bronchus to advocate removal of the affected lobe. To accomplish this early diagnosis is essential.

CLINIC OF DRS. GEORGE W. NORRIS AND DAVID L. FARLEY

PENNSYLVANIA HOSPITAL

ABSCESS OF THE LIVER

THE liver is the largest organ of the body. Its relations are intricate. It is in juxtapositional relationship with the right lung, the diaphragm, the right pleural cavity, the heart, the pericardium, the right kidney, the stomach, the pancreas, the duodenum, the colon, and the great venous and arterial blood channels. Its portal system drains the intraperitoneal viscera. It is concerned with active and passive immunity, the detoxication of poisons, the direct digestion of food, the internal digestion and handling of proteins, fats, and carbohydrates, the proper coagulability of the blood, and, in time of need, assists in the proper maintenance of the acid base equilibrium of the blood and tissues.

From the numerous relationships and diverse functions of the liver we might assume that diagnosis of hepatic disease would be easily made, yet exact diagnosis of disease of the liver, particularly early disease, is attended often with difficulty. This is true of abscess of the liver. The 2 cases outlined below emphasize this fact. It is the rule rather than the exception that the patient suffering from hepatic abscess presents a diagnostic problem. He is seen by consultants, *x*-rayed, and studied from many angles. Opinion is divided as to the diagnosis. Unfortunately, it is not unusual that necropsy settles the diagnosis.

Abscess of the liver is comparatively rare. In most instances it is a secondary condition. The primary lesion may be quite obscure. It may have healed and symptomatically direct little attention to itself. An instance is an attack of acute inflammation of the hemorrhoidal veins. After a few days it subsides.

Days or weeks later abscess of the liver manifests its symptoms; they are difficult of interpretation, and neither the clinician nor the patient may attach importance to the first condition.

Most liver abscesses fall into one of two groups, the solitary abscess caused by Entamœba histolytica, and multiple abscesses, secondary to a point of infection within the field of drainage of the portal vein.

Empyema of the gall-bladder and cholangitis may lead to liver abscess. In these cases the symptoms referable to the gall-bladder frequently are the overshadowing features. An echinococcus cyst of the liver may become infected from pyogenic organisms and form a solitary abscess. The liver with other viscera is often studded with miliary abscesses in septicemia. This type of abscess is not of clinical importance in itself, since the acute fulminating results of a septicemia which has reached this stage lend anatomic interest only to the diagnosis of local liver lesions. Direct trauma from a stab, a bullet, or a blow may cause liver abscess.

The history and findings in 2 cases of liver abscess where the studies have been completed by necropsy examination have been selected. They belong to the two most important groups, solitary or tropical abscess, and a case presenting multiple abscesses secondary to a point of infection within the field of drainage of the portal vein.

Case I.—Medical Service of Dr. George W. Norris, Pennsylvania Hospital.

H. J., aged twenty-three years; colored; male; laborer; admitted January 15, 1925. The patient was born in Jamaica. He lived for two years in Panama. For the past five years he has been a resident of Philadelphia. Since the age of fourteen he has been accustomed to taking ½ to 1 pint of spirituous liquor daily. There was no history of venereal infection. He had lobar pneumonia in 1918. He gave no history of diarrhea or other gastro-intestinal symptoms. He felt well until December 27, 1924, when he began to have a dull pain in the left side of the chest in the region of the left axilla. This pain was increased by inspiration. On January 9, 1925 he had a severe chill. Since then he had felt ill and had been unable to work. He thought he had had considerable fever. Recently his ankles had been slightly swollen.

Examination on admission (January 15, 1925): The patient is drowsy and somewhat toxic. Respirations are short and restricted. There is a severe paroxysmal hacking cough without expectoration. There is tender-

ness and cutaneous hyperesthesia over the middle of the left chest laterally, in which region a pleural friction sound is heard. Posteriorly there is marked dulness, with increased resistance over the right base below the middle of the scapula. Over this region a few crackling râles are heard. Breath and voice sounds are diminished and the former are bronchial in character. A few scattered râles are heard over the left chest with vesicular breath sounds. The heart action is rapid and regular. There is a short, harsh, late systolic murmur at the cardiac apex. Apparently there is no displacement or enlargement. There is moderate ascites. The liver is palpable 9 cm. below the ensiform cartilage and 6 cm. below the rib margin in the midclavicular line. The liver is not tender. It is soft in consistency and has a smooth surface. The spleen is not palpable. The ankles are slightly edematous. The peripheral reflexes are equal and of normal range. There is no jaundice or cutaneous eruption. The blood-vessels are soft and not sclerotic. There is no lymph adenopathy. The temperature is elevated to 103° F.; the pulse is 112.

Laboratory Findings.—Repeated urine analyses were negative; an average blood-count showed: hemoglobin, 48 per cent.; red blood-cells, 2,450,000; white blood-cells, 8200; polymorphs, 71 per cent.; lymphocytes, 13 per cent.; large mononuclears, 4 per cent.; transitionals, 9 per cent.; eosinophils, 3 per cent.; basophils, 0 per cent. Blood-cultures were sterile. The sputum was negative for tubercle bacilli. The Wassermann reaction was negative; the feces were not examined.

Report of Roentgen-ray Studies (Dr. David Bowen, January 16, 1925).—Chest: There is a considerable amount of mottled shadow over both lungs, more general over the right and more distinct over the lower left lung. The extreme base on both sides is practically free. The same may be said of the apices. From this single film I find it almost impossible to make a differential diagnosis. Tuberculosis seems quite unlikely.

1/22/25. Stereoscopic and fluoroscopic: There is considerable pathology on both sides of the chest and the condition has probably advanced since the previous examination, because at this time we can definitely state that the extreme bases are not free from pathology, but are perhaps the most affected portions of both lungs. The apices also show at this time some abnormal shadow (peribronchial thickening extending up to them), but they are unquestionably the clearer portions of both lungs. I think that this examination is also more suggestive of pulmonary tuberculosis than the previous one, but against tuberculosis is the fact that the lesions in both lungs seem to be toward the bases rather than the apices.

Course in Hospital.—The temperature showed marked variation, rising rapidly from normal or subnormal to 104° or 105° F., and as rapidly descending to the first degree. This occurred almost daily. There were no chills. The pulse showed the usual variation with the fever.

1/19/25. The pulmonary signs and symptoms were predominant. A tentative diagnosis of miliary tuberculosis was made.

1/20/25. Examination of the eye-grounds was negative.

1/23/25. The patient was seen in consultation by the surgeon. His opinion was that the patient had a generalized tuberculosis and that there were no surgical indications.

1/28/25. The diagnosis of miliary tuberculosis seems more and more justified.

2/3/25. The patient is becoming more stuporous and the signs point toward involvement of the nervous system.

2/5/25. Death.

Necropsy Report (Dr. J. R. Paul, 2973).—The liver is dark red in color and projects below the costal margin. It weighs 1550 grams. It is adherent to the diaphragm. On gross section there is a single round, well-defined abscess cavity occupying the dome of the right lobe and measuring 7 cm. in diameter. It is filled with greenish-yellow pus. Shreds of destroyed liver

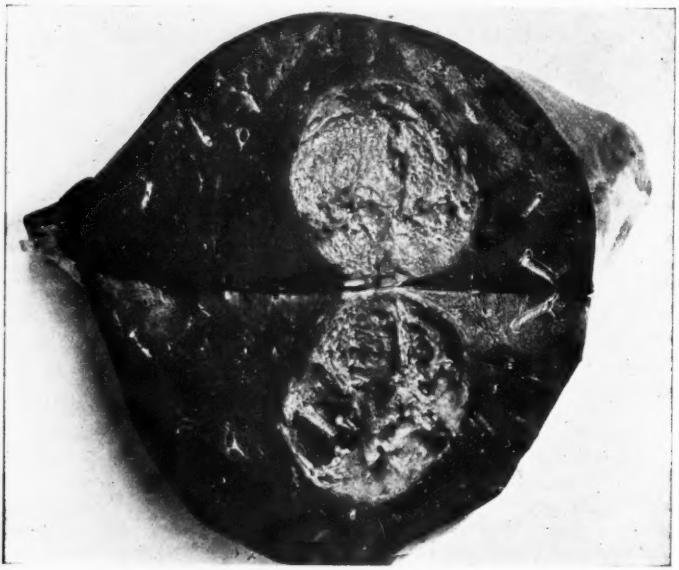

Fig. 4.—Solitary abscess of the liver, Case I.

tissue stretch across the abscess cavity and there are roughened nodules of granular necrotic material.

The lungs are pale in color. Their surfaces are mottled, showing splotched areas of consolidation. They weigh 1100 grams. On gross section there are bilateral abscesses filled with thick greenish-yellow pus. The walls of the abscess are well defined. There is comparatively little reaction in the surrounding tissue. There are abscesses in both lower lobes, and in the upper left there are small similar cavities.

The spleen weighs 180 grams. The heart shows no gross abnormalities. The intestines were examined minutely. They show no evidence of ulcera-

tion. Their walls are not thickened. There is nothing to suggest dysentery.

Summary.—Abscess of the liver (solitary amebic). Multiple abscesses of the lungs.

Discussion: Case I.—From an etiologic viewpoint the patient serves to recall that amebic liver abscess occurs more frequently in the male sex; that individuals who use alcoholic liquors habitually are more prone to the disease; that amebic abscess of the liver may develop in an individual who has had no symptoms of a preceding dysentery; that not infrequently no evidence of intestinal lesions are found at necropsy; that the disease occurs with greatest frequency in those who are living or have lived in the tropics. It should be remembered, however, that many cases have been reported which have occurred in individuals who have lived always in temperate zones.

The pathologic sequence of events probably was as follows: a cryptic amebic infestation of the intestinal tract, transfer of living amebæ to the liver by way of the portal vein, direct or lymphatic involvement of the right diaphragm, the right pleura and the base of the right lung; communication of the infestation to a bronchus, transfer to the left lung by means of aspirated material from the large bronchi or trachea. Surgical interference at a stage before the involvement of the lungs might have cured the patient.

The diagnosis of liver abscess was not reached clinically. One factor causing this was the predominance of pulmonary signs and symptoms. Acute hepatic disease and oftentimes acute disease of the gall-bladder frequently cause right-sided pulmonary signs and symptoms.

The physical signs may be those attendant upon a high position of the right side of the diaphragm, those of a pleurisy at the right base of the lung, and frequently the presence of fine crackling râles with restricted aëration. Pulmonary disease and malaria are often suspected in liver abscess. Malaria is suspected because of the frequently enlarged spleen, the chills, the hectic fever, the low leukocyte count, and the secondary anemia; pul-

monary disease because of the physical signs at the right base of the lung.

The patient under discussion had a definitely enlarged liver. This may or may not be present in liver abscess. There was no tenderness of the liver and no pain in that area. This is not unusual in hepatic abscess and as much as anything else accounts for the difficulty of diagnosis. We are always impressed by pain and tenderness, and the absence of both is apt to make us discount other symptoms.

The absence of an eosinophilia is to be noted. Because the amebia is an animal parasite we are prone to endow it with the usual blood response to such organisms, the production of an eosinophilia. The eosinophils in amebic dysentery and its complications are usually not increased above the normal differential proportions. This is to be remembered.

The correct diagnosis of hepatic abscess might have been determined by puncture of the liver. This is frequently done in tropical countries. It is not without risk, but is justified under proper indications. The caliber of the needle should be large enough to permit the flow of thick pus.

When large amounts of hepatic tissue have been destroyed the excretion of urea may be diminished. At the same time the ammonia nitrogen of the urine may be increased because the catabolism of protein by the liver is halted before the stage of final breaking down to urea is reached.

Examination of the stools might have shown the presence of Entamœba hystolytica or its cysts.

Case II.—First admission. Medical service of Dr. George W. Norris, Pennsylvania Hospital.

B. M., aged thirty-four, Italian; male; laborer. Admitted August 12, 1922. His chief complaint was pain in the back. Family history and past medical history were negative. Recurrent attacks of pain in the back, accompanied by swelling of the abdomen and tingling sensations in the legs, had come on suddenly one month previous to admission. All examinations were practically negative. No satisfactory diagnosis was reached and he was discharged at the end of ten days with apparent improvement in his symptoms. The diagnosis was myositis of the lumbar muscles.

Second admission, November 16, 1922: At this time he complained of chills and fever, beginning three weeks previously, and accompanied by epi-

gastric pain. The chills came at no regular intervals, occurring sometimes twice in the same day. Slight cough was present, with thin expectoration. Soreness was present over the right hypochondrium. For the past fifteen days he had been jaundiced. He had lost considerable weight.

Previous medical history was negative except for the attack of illness described on first admission to the hospital.

Physical Examination.—The patient is an adult Italian male, about thirty-four years of age. He is quite toxic. The skin is clammy. He appears to have lost weight. There are no abnormal physical signs about the eyes, ears, nose, or mouth except a moderate degree of pyorrhea alveolaris. There are occasional small lymph-nodes palpable in the anterior cervical chains. Chest expansion is limited at the right base. Breath sounds anteriorly are somewhat harsh at the apices. There is slight impairment to percussion over the right base. On deep inspiration a few fine râles are audible there. No abnormal cardiac signs are present. Examination of the abdomen shows slight rigidity of the right rectus abdominalis. There is slight general abdominal tenderness. The liver is indefinitely palpable 4 cm. below the xiphoid cartilage. There is an indefinite mass palpable in the right hypochondrium. The spleen is not palpable. Extremities are negative.

Laboratory Findings.—The Widal test was negative; urinalyses were negative; blood-counts 11/14/22: Hemoglobin, 68 per cent.; R. B. C., 4,540,000; W. B. C., 8650. Differential count, polymorphs., 76 per cent.; lymphocytes, 18 per cent.; L. M., 4 per cent., eosinophils, 2 per cent.

11/18/22: W. B. C., 16,400.

11/19/22: W. B. C., 12,100.

11/21/22: W. B. C., 11,700.

11/27/22: W. B. C., 17,000.

Four examinations of the blood for malarial parasites were negative. Two blood-cultures were sterile. The examination of sputum for tubercle bacilli was negative.

Course in Hospital.—The temperature pursued a hectic course and patient showed signs of increasing emaciation with rapidly progressing anemia.

November 20th: A tentative diagnosis of cholelithiasis, with accompanying Charcot's fever, was made. He was transferred to the surgical service.

November 22d: An upper abdominal exploratory operation was performed in which both gall-bladder and liver seemed to be negative. Drainage of the gall-bladder was done. The patient continued to do badly following the operation.

December 10th: Signs of fluid suddenly developed in the right chest. He was tapped, and a large quantity of orange colored purulent fluid was aspirated. Cultures of this fluid showed enormous numbers of colon bacilli and streptococci.

December 14th: Thoracotomy was done. A small rent was found in the diaphragm beneath which was an abscess cavity involving the right lobe of the liver. This abscess was drained through the chest cavity. The patient died two days after the operation.

Necropsy Report (Dr. J. R. Paul).—On opening the chest a massive empyema cavity was exposed on the right side, containing a fair quantity of

orange-colored purulent fluid. The small rent in the diaphragm, noted at operation and denoting the point of rupture of a liver abscess into the pleural cavity, was easily demonstrable. In the abdomen enlargement of the liver was noted with localized adhesions about the recent gall-bladder operation.

On removing the stomach and duodenum a retroperitoneal abscess was exposed in association with the portal vein, which was found to be thrombosed throughout its entire length. The thrombus was infected and suppurating, and the vein wall greatly thickened. Thrombosis of many of the mesenteric

Fig. 5.—Multiple abscess of the liver, Case II.

veins and pelvic veins was also present. The appendix was quite normal, and the only demonstrable lesions involving the gastro-intestinal tract was one small rectal polyp and a group of large thrombosed hemorrhoids. The liver proved to be studded with a great number of abscesses scattered through its substance containing thick yellow pus, from which the same type of organisms were cultured as were noted in the fluid aspirated from the chest.

The interesting features shown by the microscopic sections were the thrombi which were seen in the pelvic and mesenteric veins. Well-marked

organization with fibroblasts growing in from the vein walls was demonstrable. Infection in association with these thrombosed veins was well marked in the form of perivascular lymphadenitis. Bacterial stains of the sections showed the presence of streptococci and bacilli in perivascular lymph-spaces associated with the hemorrhoidal veins.

Discussion: Case II.—The second patient typifies the majority of cases of hepatic abscess encountered in temperate zones—multiple wide-spread abscesses, usually involving the right lobe of the liver, and secondary to pyogenic lesions elsewhere.

The patient was under hospital observation and study for a period of ten days. No satisfactory diagnosis was reached. Sixty-five days later he was again studied in the hospital. A diagnosis of cholelithiasis with accompanying Charcot's fever was made. An exploratory operation was done. The gall-bladder and liver at operation showed no gross evidence of disease. However, the gall-bladder was drained. Eighteen days later the right pleural cavity was found to contain pus from an abscess of the liver which had ruptured through the diaphragm. Thoracotomy was done and the hepatic abscess drained through the thorax. The patient died two days later. At necropsy a group of large thrombosed hemorrhoids with secondary thrombosis of the portal vein and resulting multiple liver abscesses was found.

This patient again shows the difficulty of diagnosis of liver abscess. With the liver under direct observation at operation the diagnosis was not apparent. The initial lesion, the infected hemorrhoids, were not taken into account in this clinical study. The condition of the liver manifested itself later in the course through pulmonary symptoms and signs. Malaria was suspected, as shown by repeated examination of the blood for the plasmodium.

At the time of the patient's first admission he was suffering probably from the local pelvic condition, thrombosis, and infection of the pelvic veins. This no doubt accounted for the pain in the back and the diagnosis of lumbar myositis.

In neither of the cases were functional liver tests performed. In our hands the Rosenthal test, using phenoltetrachlorphthalein,

has been the most satisfactory test. Aside from the difficulty of its performance its chief drawback has been that it shows delayed excretion of the dye only in very pronounced hepatic lesions.

During the past twenty-five years the diagnosis of abscess of the liver has been made in 52 patients at the Pennsylvania Hospital. (This does not include, of course, the miliary abscesses due to septicemia, nor abscesses above and below the liver.) During the same period (twenty-five years) a total of 124,430 patients have been admitted to the hospital wards. This is an average of about 2 patients each year with liver abscess. This rarity of occurrence of liver abscess shows the ability of the liver to withstand infection. This has been proved also experimentally.

Six of the 52 abscesses were caused by Entamœba histolytica; 46 were of pyogenic origin. Necropsy was performed in 29 cases. In studying the records where necropsy was done, it was possible usually to trace the pathologic sequence leading to the formation of hepatic abscess. The most frequent primary lesion was appendical disease, with thrombosis or embolus through the channel of the portal system, and secondary multiple hepatic abscesses. The next most frequent cause was a suppurative cholangitis secondary to disease of the gall-bladder. Two patients had abscess of the liver secondary to thrombosed hemorrhoidal veins. One of these occurred in a patient with a syphilitic stricture of the anus. One abscess was secondary to a perforating duodenal ulcer; another resulted from acute pancreatitis; one from a chronic pelvic peritonitis in a female; one occurred in the course of a typhoid fever from ulceration of the intestines and involvement of the mesenteric veins; one occurred after intestinal obstruction; 3 cases were of amebic origin. In 5 cases the exact pathologic sequence was not apparent from the available records.

Frequently abscess of the liver was not diagnosed until necropsy. Malaria was often noted as a tentative diagnosis. Many of the cases received quinin at some time during their course. Primary pulmonary disease, especially of the right lung and pleura, was often suspected. The spleen was frequently en-

larged. Its intimate connection with the liver and the portal system might predict this frequency of enlargement in hepatic disease. Enlargement of the spleen in the presence of an acute infectious process should lead one to consider hepatic disease as well as malaria and typhoid fever.

The importance of careful and detailed questioning of the patient for evidence of a primary lesion was evident. The importance of the history in any obscure condition again stands out. Tenderness and hyperesthesia over the liver area was present in many cases.

An exploratory laparotomy was done in 2 patients, where, under direct inspection of the liver, the surgeon was unable to determine that an abscess was present. In neither case was the liver needled. This evidently should have been done.

Finally, it may be said that abscess of the liver is a comparatively rare condition; that the abscess usually develops from a primary lesion within the field of drainage of the portal vein; that diagnosis is often difficult; that diagnosis is much easier if symptoms of the primary condition are elicited; that these symptoms of the primary condition often constitute the correct key to proper diagnostic reasoning; that pulmonary disease and malaria are frequently wrongly diagnosed in hepatic abscess; that infection of the liver with abscess formation occurs with difficulty; that it is probable that a massive dose of the infectious material is necessary to produce a liver abscess; that embolus and thrombus of abdominal veins with direct extension to the liver occurs often in the type of multiple abscesses of the liver; that at operation the external appearance of the liver may give no indication of an abscess within its depths; that when evidence is strongly in favor of liver abscess careful search should be made for the abscess by exploratory puncture at the time of operation; that the clinician should remember that physical signs or even positive evidence of disease of the base of the right lung may be secondary to disease about or within the liver.

CLINIC OF DR. O. H. PERRY PEPPER

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ON THE NEGLECT OF ONSET SYMPTOMS

I. Varicocele as the First Sign of Sarcoma of Kidney.
II. Pain in the Breast from Esophageal Ulcer.

IT is a truism of both medicine and surgery that successful therapy depends in the final analysis on early diagnosis. The internist has emphasized it in tuberculosis and diphtheria; the surgeon, in carcinoma of the breast or stomach, in appendicitis, and in internal hemorrhage. The reasons in each of these instances are clear, for in each there exists a treatment of considerable efficacy if only it is applied sufficiently early. The principle, however, is of general application, and our every effort should be directed to the study of early signs and symptoms in all types of disease.

Obviously, it is upon early symptoms or early changes in the physical examination or in laboratory investigation that an early diagnosis must depend. This being so, it is equally obvious that if we are to make an early diagnosis we must not only elicit these early evidences of disease, but, having done so, we must properly interpret our findings. This sounds simple, but it is far from being so, and in this direction lies one of the most glaring weaknesses of medicine today. Sometimes we fail to elicit the evidence, more often we fail to interpret it correctly.

This subject is very much in our minds today because of the emphasis which is being given to so-called "health examinations"; the routine annual examination of the supposedly healthy. If we often are unable to make an early diagnosis in a patient who comes to us on account of ill health, how much more difficult it must be for us properly to examine and correctly to diagnose the unsuspected illness of one who considers himself in perfect health.

We must learn to evaluate such symptoms as loss of appetite; in one instance it may be the earliest hint of gastric carcinoma, in another a neurosis pure and simple. How promptly should insidious loss of weight deserve careful attention? It may be due merely to an increase in cigarette smoking, or it may signify the appearance of some potentially serious disease. Care and thoroughness will go far to elicit the early symptoms and signs of disease, but we need to study the possible significance of these perhaps apparently trifling signs and symptoms that, once having elicited them, we may give them their proper weight and be guided to an early correct diagnosis. It is from this point of view that the following cases are presented. Each is an old story, but one about which we need occasionally to be reminded.

Case I.—Mr. J. M. J., aged fifty-nine years. Referred by Dr. Joseph C. Yaskin.

Chief Complaints.—Loss of appetite and loss of weight. The patient was intelligent and co-operative. He dated the onset of his trouble as about three months previous, at which time his appetite rapidly became extremely poor and he commenced to lose weight. He consulted a physician, who shall be nameless, for if the patient's statement is to be trusted, no physical examination was ever made. It was probably already too late to save the patient's life, but this scarcely excuses the omission of a physical examination.

The physician's attention was caught and held by an enormous goiter which was present. This had first been noticed six years before as a small mass, but within three years it had reached its full size, and during the next three years it did not enlarge any further, nor did it produce any symptoms whatever. This goiter so dominated the picture that the physician went no further, but attributed the patient's loss of appetite and weight to the goiter, and advised the patient to go to Cleveland for its removal. It was then that the patient consulted his friend, Dr. Yaskin, and was sent to me for an opinion.

The history was meager; the symptomless goiter had been present for six years. Six months previously he had rather suddenly developed a varicocele on the left side; this was painful for a time, but was relieved by local applications and a suspensory. Three months ago the loss of appetite appeared and the loss of weight commenced. By the time of his visit to my office his loss of weight had reached 30 pounds. He was, however, still overweight, having been a very obese man.

He stated that he had been a very healthy man, but that for several years his blood-pressure had been somewhat high, once 180; and that he had once been refused life insurance on this account. Careful questioning, both at this time and later, elicited no further symptoms. He denied all venereal disease.

At this stage in the study of the case the outstanding items were:

1. Large symptomless goiter present six years.
2. Raised blood-pressure (180) for several years.
3. Large varicocele (left side) present six months.
4. Loss of appetite and weight for three months.

It is always interesting in retrospect to review a case record and try to interpret the symptoms in the light of the later findings. In this instance when this is done it is the varicocele which becomes the most important of these symptoms. The rest of the story can be told very briefly. A routine physical examination revealed in addition to the goiter a large firm mass in the region of the left kidney, the presence of a moderate ascites, and of a definite left-sided varicocele. The urine on several occasions revealed a moderate number of red blood-cells; the blood-count revealed some secondary anemia; the Wassermann test was negative.

In view of these findings the diagnosis of "neoplasm of the left kidney" was made. A roentgenologic study after a bismuth enema proved the mass to be independent of the colon. On laparotomy an enormous tumor mass was found extending back toward the left kidney, but also involving the retroperitoneal lymph-nodes. Dr. George P. Muller, who performed the operation, removed as much as was possible, and after the operation Roentgen-ray treatment was vigorously given. The patient, however, has gone slowly down hill. The histologic study of the tumor resulted in a final diagnosis of "spindle-cell sarcoma."

Reviewing the case, it is obvious that by the time the patient came to me the diagnosis was clear and no special credit attaches to me; unfortunately, it was too late. That it was not made sooner was due (1) to the failure of the physician to perform an ordinary routine physical examination; (2) to his losing sight of other possibilities in his attention to the goiter which, while enormous, was associated with neither pressure symptoms nor disturbed thyroid function; (3) to his failure to appreciate the possible significance of the suddenly developed varicocele a few months previously.

What is there about the development of such a common condition as varicocele to excite our interest in this case? Varicocele occurs so frequently as to be accepted without comment in many instances, but in this patient there were certain features of the varicocele which made it a very important symptom, strongly suggesting a renal tumor. In the first place, varicocele commonly occurs before the age of thirty and has in the majority of instances ceased to be a troublesome matter before the age which our patient had reached. Furthermore, as a rule, it develops slowly. The rapid development of varicocele at any age or its development at all in a man past fifty should immediately arouse the suspicion of kidney neoplasm. The vast majority of so-called idiopathic varicoceles occur on the left side. This has been variously explained; by some as due to the anatomic differences in the spermatic veins. On the right the spermatic vein enters the inferior vena cava at an acute angle; on the left it enters the renal vein at a right angle. Others believe that the frequency of left-sided varicocele is due to the absence of valves in the left spermatic vein, and still others attribute it to the pressure of the heavy sigmoid in individuals with constipation. Whatever the correct explanation, it only interests us in the present discussion in so far as it makes a left-sided varicocele apparently less suspicious than a right-sided one. Some have gone so far as to say that a right-sided varicocele should be suspected of being symptomatic of a growth in the kidney region, even though it occurs in the age period in which idiopathic varicocele is common. In the patient being discussed the varicocele was left sided, and so perhaps was not so immediately suggestive, but its rapid onset at the age of fifty-nine should have been sufficient to excite the fear of its being the evidence of back-pressure from a neoplasm in the kidney region. There is not complete agreement as to how the kidney tumor brings about the symptomatic varicocele. Some think that the tumor presses directly on the spermatic vein; others, that the varicocele does not occur until metastasis, to lymph-nodes lying on the vein, has occurred. Another theory believes the malignant process extends into the renal vein and cava and so causes the back pressure. The theories only interest

us secondarily. The fact is important, and in this case the development of the varicocele should have led to investigation of the left kidney, with perhaps the discovery of the kidney tumor early enough for cure.

One final word about the goiter. It is hard not to allow one's attention to be centered on a lesion so obvious and so enormous, but in the absence of all evidence of pressure or of thyroid dysfunction it was improbable that a loss of weight and appetite could be due to this cause.

Case II.—Two years ago a woman forty-nine years of age was referred by Dr. Floyd E. Keene for investigation on account of an annoying persistent sticking pain and tenderness at the point where the right breast joined the chest wall. The pain was not severe and was only somewhat annoying, but back of the patient's desire for investigation and treatment was a very marked cancer phobia which led her to wish to exclude every possibility of this condition as far as possible. She had just had a gynecologic examination before coming to me.

The only other complaints were a general feeling of depression and the fact that she tired easily. She had lost 8 pounds during the previous year. Her previous medical history was unimportant. In the family history was a recent death from carcinoma which in part caused the phobia already referred to. The patient's own suspicion was that there was cancer of the right breast. After taking the history one could not help being impressed with the fact that the patient was an extremely nervous woman of the high strung socially overactive type. Also that except for the constancy of the slight pain at the inner margin of the right breast and the loss of weight there were no definite symptoms whatever; the pain was uninfluenced by position, weather, food, deep breathing, or, in fact, by any ascertainable factor. It varied from day to day in intensity, but was almost constantly present to some degree.

Such constancy of even a trifling pain, even in the most neurotic individual, makes it a matter worthy of the most careful search. Furthermore, the patient insisted on the most thorough examination because of her fear of cancer.

The routine physical examination was entirely negative except for a very small, palpable lymph-node just above the right clavicle. The right breast was absolutely normal to physical examination. The patient seemed to locate the pain within the chest rather than in the breast.

The routine blood-count and urinalysis were in every detail normal. A Wassermann had previously been reported negative.

In view of these negative findings I was at a loss to explain the pain, and might well have dismissed the matter as the negligible complaint of a neurotic woman. Fortunately, the patient insisted on further study, and an *x*-ray examination of the chest including the esophagus was undertaken.

Dr. H. K. Pancoast, at the University Hospital, made the following report:

"The examination of the chest was negative.

"The examination of the esophagus showed that semisolid jam and bismuth mixture passed readily through. A capsule lodged for at least a minute at the level of the fifth or sixth thoracic vertebra. It was dislodged by one swallow of water and then passed readily down into the stomach. The capsule would probably have remained at the point of lodgment until dissolved had it not been forced down. The exact nature of the obstruction, which is no doubt slight, is uncertain."

As a result of this discovery it was decided to have an esophagoscopic examination performed. The patient entered the University Hospital and was studied by Dr Chevalier Jackson, who made the following report:

"In the middle third of the esophagus there is a chronic inflammatory condition of the mucosa with patches of bleeding epithelial erosion; gastric mucosa slightly inflammatory with slight erosions of the epithelium in the neighborhood of the esophageal orifice; other portions of stomach not explored.

"Esophagoscopic diagnosis: Chronic esophagitis.

"Remarks: Bismuth subnitrate dry on the tongue in small doses—5 to 10 grains after all meals and after all foods or liquids that may be taken between meals—is the best local treatment for this condition. Food should be bland and unirritating, free from pepper and spices, and should be thoroughly masticated; rough foods should be avoided. The nervous system should have care and especially rest. Endocrime disturbances if present should be cared for. The usual origin of this condition is temporary food stasis from spasm. The esophagitis often persists after the static condition has disappeared, and is often slow to improve even under treatment. There is no cancerous lesion in the pharynx, hypopharynx, larynx, or esophagus."

The location of the lesion which was found was directly at the level of the patient's pain, and it seemed reasonable to assume that the esophageal lesion was the cause of the pain.

Nevertheless, further questioning failed to elicit any relation of the pain to swallowing.

Dr. Jackson's opinion that the condition was not cancerous has been borne out by subsequent events. The supraclavicular gland was removed, fearing that it might show a metastatic process, but it revealed no carcinoma. The treatment suggested by Dr. Jackson was carried out and the patient has gained considerable weight, has been relieved of the pain, and has become much less nervous; altogether she has improved very markedly.

Reviewing this case in retrospect, the interest attaches to the explanation of the pain which was finally arrived at. Once the lesion in the esophagus was found, everything became obvious. The patient was exactly of the type who according to Dr. Jackson develop this form of esophagitis above an area of spasm. Her pain was located in the zone in which referred pain from the esophagus occurs. It was all very easy in retrospect, but at first the patient's cancer phobia and nervousness and the fact that she located the pain in the breast made it very tempting to consider the pain in breast as a neurotic manifestation localized in the breast through fear of breast cancer as a result of the death within the year of a relative and a friend, both from cancer of the breast.

In this case the fortunate discovery of the true explanation of an early symptom perhaps prevented more serious developments. In this case the loss of weight was relatively unimportant, while the persistent pain always localized in one spot was the signal which should have aroused suspicions even before the *x*-ray revealed the esophageal lesion.

Examples might be multiplied, but these two will be sufficient to illustrate the point which is being emphasized. The current literature contains many excellent articles stressing the early symptoms of this or that disease, and the need of their prompt recognition for what might be called a therapeutically useful diagnosis. Bunker[1] has recently drawn our attention to the irritability and change of character which are the most important

[1] Amer. Jour. Med. Sci., March, 1926, 171, 386.

of the incipient symptoms of paresis. Frazier and Spiller,[1] in reporting 14 consecutive cases of spinal cord tumor, emphasized the frequency with which pain is the first symptom and in almost equal frequency with which this pain is incorrectly attributed to other causes. Chevalier Jackson,[2] in a plea for early diagnosis of carcinoma and sarcoma of the esophagus, writes, "It would be better for suffering humanity if all mention of symptoms were omitted with the exception of those listed as 'early symptoms.'" This point of view might with equal justice be applied to many varying conditions.

We must rewrite the symptomatology of disease just as often as progress grants us further knowledge into still earlier symptoms and new methods of eliciting signs and laboratory evidences of disease. Too much emphasis cannot be placed on this subject, not only in the field of medicine, as it concerns the patient who comes complaining of ill health, but also in the field of prevention of disease by the routine periodic examination of those supposedly healthy.

[1] Jour. Amer. Med. Assoc., 1922, 79, 24.
[2] Amer. Jour. Med. Sci., 1925, 169, 625.

CLINIC OF DR. EDWARD A. STRECKER

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PARESIS SINE SYPHILIS

Introduction.—The demonstration of the treponema in the brain cortex of paretics by Moore and Noguchi in 1913 was the final link in the chain of evidence which determined that lues was the sole cause of paresis. Seven years previous to this brilliant contribution the researches of Wassermann, Neisser, and Bruck on syphilitic fluids decreased the considerable margin of error which had existed in the diagnosis of paralytic dementia. However, there still remains a diagnostic problem. From time to time there are reported instances of non-luetic paresis which bear a striking resemblance to true paralytic dementia. Alcohol, lead, and other toxic agents, and certain organic nervous involvements, notably multiple sclerosis, frontal lobe disease, and epidemic encephalitis, may give the clinical imprint of parenchymatous brain syphilis. The cases which are about to be reported probably imitate paresis more faithfully than any other group, and should be kept in mind as a possible source of diagnostic error.

PRESENTATION OF CASES

Case I.[1]—J. W., female, aged fifty-seven. The family history of this patient is largely unobtainable, but so far as known it is negative. She was the second eldest in a family of 5 children. Information concerning the birth, infancy, and childhood is unobtainable, but she is said always to have enjoyed excellent health. Completed common school grades at the age of fourteen, when she took up work in a textile mill. She married at the age of nineteen. There were 3 pregnancies and no miscarriages. Two sons are living and in good health. The eldest child, a daughter, died at eight months of malnutrition.

Her husband died in 1917, after a two-day illness of sudden onset which was diagnosed "kidney trouble." After his death the patient was morose, sensitive, and discontented.

[1] This patient was studied with Dr. Gordon Willey.

The present illness dates from about May 1, 1923, when without antecedent symptoms she began to complain of dizziness and unsteadiness. There were four severe falls, but without unconsciousness or definite evidence of injury. At times her tongue seemed thick and she swallowed as if something were irritating her throat. She became careless and indolent. At Atlantic City in July she became excited and confused; a few days later she seemed dejected, talked but little, and was worried about her difficulty in walking. On August 1st she became suddenly talkative and exhilarated; said that she was wealthy; planned to spend large sums of money for houses and jewelry; wanted to have her hair bobbed, to use a lip-stick to make herself beautiful, and to marry her physician. She telephoned various stores ordering useless articles, and was profane and obscene when opposed. She then began to complain of a film over her eyes, but said that she would kill herself before she would go to a hospital. Her appetite was voracious, and on one occasion she ate 2 quarts of ice-cream in one day.

On admission to hospital she was euphoric and elated, recognized the physician as an old acquaintance whom she was to marry, and this delusion persisted. She also promised nurses large sums of money. Physical examination showed obesity. The teeth were in poor state of repair and several were missing. The eyes, ears, nose, and throat were negative on gross examination. The lungs were clear. The heart was normal in size and position. There was a soft systolic murmur at the apex, transmitted to the axilla, and moderate radial and temporal arteriosclerosis. The systolic blood-pressure was 134, the diastolic 84. The abdomen was flabby and protuberant, but no tenderness or spasm was manifested.

The left arm at first seemed to show some spasticity and weakness, later this finding could not be confirmed and definite pyramidal tract signs were lacking. The normal associated movements were present and no abnormal movements were noted.

The abdominal reflexes were not present, but the abdominal wall was relaxed and flabby. Plantar irritation gave but little response on either side. All tendon reflexes were equally exaggerated, but without clonus. Dysmetria was shown in finger-to-nose and in heel-to-knee tests, but for several weeks the Romberg was negative. The sense of position and of vibration might have been moderately disturbed, but this could not be accurately determined because of the mental state. Tactile discrimination and localization could not be plotted accurately, but the patient responded quite normally to pain, touch, and extremes of heat and cold over the entire skin surface. The vision was moderately decreased, but the visual fields could not be plotted. The eye-grounds were repeatedly examined and were negative except for moderate changes in the vessels due to arteriosclerosis. Ocular movements were limited in a vertical direction at both extremes of motion. The pupils were equal in diameter; the left was irregular, and both reacted sluggishly to light and equally so to distance. Apparently there was no sensory, motor, or secretory abnormality in the distribution of the remaining cranial nerves. The speech, at first negative, became later thick and indistinct, but without any suggestion of bulbar involvement. There were no vasomotor or trophic abnormalities found, and no loss of sphincter control until later.

x-Ray of the skull was negative as to bony parts and as to sinuses, mastoids, and sella turcica. Examination of the ears and caloric tests by Dr. Fischer proved difficult because of lack of co-operation on the part of the patient, but Dr. Fischer felt that the findings indicated a rather diffuse cerebral condition, such as might be based upon general paresis or cerebral arteriosclerosis.

Gynecologic examination revealed a smooth mass about 3 inches in diameter apparently lying in the left broad ligament. The uterus was small and fixed and the cervix was clean.

The urine showed a trace of albumin and of indican at all examinations, and granular and hyaline casts were found in small numbers. The erythrocyte count was 4,060,000, with a hemoglobin of 80 per cent., which rose to over 5,000,000, with hemoglobin 90 per cent. The leukocyte count was 8900 and increased to 16,000, and later 18,000, with an increase in percentage of polynuclears from 70 to 77 per cent. Otherwise the differential count was negative. The blood chemistry showed urea nitrogen 15.0 mgm., blood uric acid 3.0 mgm., and blood sugar 0.105 per cent.

The serologic examinations were frequent and interesting. From Laboratory B the laboratory reports on blood and fluid were consistently negative with both antigens. From Laboratory A the report was returned 4 plus with 0.5 c.c. fluid on one occasion, otherwise this was also negative. The blood was tested four times and the fluid four. The first puncture report read 1 cell, positive Noguchi and Pandy, and a mastic test of 0110000000. The second fluid contained blood. The third gave 3 cells, negative globulin, albumin, etc. The last blood Wassermann, done after a provocative injection of neo-arsphenamin, was negative, and the fluid at this time contained 5 cells and was entirely negative for albumin, globulin, etc.

The mental examination showed considerable fluctuation in mood. With an elation and euphoria on admission, she later gave expression to ideas of persecution and abuse, and finally said that she felt sad and hopeless. She told of having been in a State Hospital, which was not true, and said that she was out of

her mind. She was approximately oriented for time, but disoriented for place and person. Her remote and recent memory were spotty and she filled gaps by obvious fabrications of an expansive nature. Her comprehension was poor, as also was her attention, and her solutions of arithmetical problems were largely incorrect.

Deterioration of mind and of conduct were rapid. Within two weeks she became untidy and careless of her appearance. In a month she was indifferent, emotionless, and with an expressionless face. Seldom spoke. Was quite unsteady and staggered, but without general weakness.

In two months there was marked inactivity, and general muscular weakness, with a persistent diarrhea, which did not respond to any form of treatment. On one occasion there was dysphagia. With the diarrhea a profuse purulent vaginal discharge set in uninfluenced by irrigation. Mentally, confusion, clouding, and deterioration were prominent.

She died October 19, 1923, ten weeks after her admission. For several days before her death there was an irregular septic fever. The cause of death was given as ulcerative colitis and tubo-ovarian abscess.

General autopsy findings (Dr. Farr, October 19, 1923):

Good nutrition, with excess of abdominal fat.

Heart not enlarged; moderate fatty deposit; no valvular lesions. The beginning of the aorta is slightly leathery, suggesting early atheroma; the vessel is elsewhere normal.

Moderate emphysema of lungs with hypostatic congestion.

The kidneys show evidence of chronic interstitial nephritis; slight for most part, but with focal areas of more advanced sclerosis.

The liver is normal aside from few local capsular lesions.

The gastro-intestinal tract in general is negative; there is moderate enlargement of solitary follicles of large intestine.

The left broad ligament contains a cyst filled with putty-like material in smears from which no organisms are demonstrated. Vascular adhesions about this tube and ovary suggest previous infection.

Many of the organs show evidence of cloudy swelling.

Summary: Old tubo-ovarian abscess; otherwise no somatic lesions of importance, allowance being made for patient's age.

Central nervous system: The findings in the brain (Dr. Taft) are as follows:

The specimen is a medium-sized brain. On the inner surface of the left half of the dura is a thin membrane, representing a chronic internal hemorrhagic pachymeningitis. This membrane extends over the entire convexity of the brain on the left, but is notably thicker over the frontal region and over the occipital convexity than elsewhere. The pia-arachnoid is slightly hazy over both hemispheres, but this is greatest in the pre-Rolandic regions, where there is also slight edema. The summits of the convolution are not well approximated over both the frontal and central regions. This suggests a degree of atrophy.

The basal vessels are small and show no evidence of pathologic change on gross examination.

In the cerebellum there is only some pial thickening over the inferior vermis.

On making frontal sections through the whole brain, a small cyst of softening appears in a narrow annectant gyrus between the second and third frontal convolutions on the right side.

Sections were taken from twenty-one areas of the cerebral cortex, following in part Campbell's selection for his studies.

Most of these sections show slight fibrous thickening of the pia, with some fibrous thickening of the walls of many pial vessels; in others there is focal hyaline change in the wall, with some calcification.

The marginal glia of the cortex is moderately increased in nearly all the sections studied.

There is scattered thinning out of the large pyramidal cells in many sections and a marked axonal reaction is present in all Betz cells, the large motor cells in the pre-Rolandic region. The change noted is characterized by swelling, chromatolysis, and an eccentric position of nucleus. This is a secondary cell change, and signifies a primary injury or degeneration of the axone in some part of its course.

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Glia cell increase is seen in the white substance of all sections, varying in degree in different brain areas.

Rarely there are a few pigmented phagocytic cells in some of the perivascular spaces.

Sections from the spinal cord show only a moderate increase in glia cells. Special staining does not reveal any tract degeneration. In the medulla there is a similar glia reaction with some swelling and chromatolysis present in the larger cells. In the basal region there is considerable cellular gliosis, and a notable degree of arteriosclerosis seen in the lenticular nuclei with slight calcification in some vessel walls on the right, and on the left a much greater degree of vascular change associated with two small areas of softening in the left putamen.

Small calcareous granules are present about some of the vessels of the thalamus, while the subthalamic region represented by the red nucleus and substantia nigra shows relatively little change.

The most extreme degree of calcification appears in the cerebellum, involving many of the larger vessels and capillaries. This change is particularly marked in the region of the dentate nuclei. Mulberry granules appear in the cortex of these areas. In the cortex of the cerebellar lobes the pia is considerably thickened by increase in connective tissue; there are focal areas of atrophy, affecting particularly the molecular layer, and there is an increase of glia cells in the white substance.

To summarize, the chief findings are:

1. Slight fibrous thickening of the pia with arteriosclerosis and occasional deposits of calcium in vessel walls.
2. Increase in marginal glia fibers.
3. Moderate thinning out of large pyramidal cells of the cortex.
4. Axonal reaction affecting the Betz cells and the large pyramidal cells.
5. Considerable general arteriosclerosis with calcification of vessel walls in basal region and cerebellum.
6. Moderate diffuse increase of glia cells in white substance of both brain and cord.
7. A small cyst of softening in the right frontal region.

Discussion of Neuropathologic Findings.—The subject of calcification in brain tissue has recently received some special notice in an article by McAlpine in Brain (October, 1923). He particularly studied material following epidemic encephalitis. In 6 cases dying in the acute stage and in 3 a year or more after the original attack, all but 1 showed calcification in the globus pallidus, and in some there were similar findings in the cerebellum.

Calcification was found in the acute stage after only four days' illness.

Age plays no part, as the cases averaged from seven days upward. The earliest deposits usually appear between the media and the adventitia. That this finding is not peculiar to epidemic encephalitis is granted, as the author found similar changes in tissues from other diseases.

Some years ago one of us studied material from a group of cases diagnosed general paresis; one case from the number showed only vascular calcification of this type and was without findings of paresis. The individual had been a painter for thirteen years and lead was considered as a possible etiologic factor. The mental symptoms had suggested paresis. More recently vascular calcification in the basal nuclei and cerebellum have been seen, without uniformity of disease causing death.

McAlpine says further as to causal relation: "It seems evident that a toxic process, either bacterial or gaseous, acts on the vessel walls, and either directly, or by causing hyaline degeneration, or by altering tissue fluids circulating in lymph-spaces of the vessels, causes a modification in the normal stage of blood calcium and permits a deposit of calcium salts within the vessel walls."

It is well recognized that deposit of calcium salts is very frequent in any tissue which has undergone hyaline change.

Warthin says: "Calcification always indicates severe metabolic changes of the tissue and the death of the cells in human pathology." He states further that it is not a precipitation due to change in the blood. Increase in calcium content of the blood is not essential; there must also be atrophy or hyaline change in the tissue.

Gideon Wells concludes that CO_2 is an important factor in the solution of calcium salts in the blood, and when there is oversaturation with calcium, it is deposited where CO_2 is least abundant.

Working experimentally on calcification, Klotz found that collodion sacs containing fat or fatty acids, when inserted into the peritoneal cavity of a rabbit, would in a few days contain amounts of calcium far in excess of that found in the body fluids of the animal.

Case II.—H. M., a white, single male, aged fifty-three, with a negative past history except for an attack of gonorrhea when he was twenty-one years of age and a distinct alcoholic history for a period of from five to ten years, was well until January 1, 1925, when he had a nocturnal convulsion. The attack lasted about twenty minutes, when he again fell asleep and awoke the next morning feeling fairly well, although he did not remember having had a convulsion. After this episode he worked regularly until February 17, 1925, when he had a second nocturnal attack, but during this attack he got out of bed and fell to the floor; he does not remember anything about this attack, but was told it lasted about twenty minutes.

On April 1, 1925 he went out to do some target shooting, and while assembling his rifle had a third attack. Immediately after this attack he became confused and remained so about half an hour. About April 3, 1925 he was admitted to the University Hospital at Ann Arbor, Mich., where he remained for three days. During his stay at the hospital he had repeated examinations of his blood and spinal fluid, and the reports were negative. The examinations of his urine, eyes, and roentgenograms of his head and back were negative.

He came to Philadelphia about May 15, 1925 and worked steadily until May 25, 1925, when at night while asleep he had an attack, and on the following day had a spell on the street during which he fell and became unconscious. On August 1, 1925 he had an attack, and several days later had another during the day. In the last two spells he had incontinence of urine.

From January 1, 1925 until September 10, 1925 he had thirteen convulsive seizures associated with unconsciousness—four during sleep and nine diurnal. He has not had an attack since September 10, 1925, feels well, and works every day.

He was admitted to Jefferson Hospital, Philadelphia, on September 16, 1925 and left on September 24, 1925. Two spinal fluid and two blood examinations were made at Jefferson, and all showed negative Wassermanns. One spinal fluid examination showed 4 cells and the other none.

Examination: A fine tremor of the hands, lips, and tongue is easily noted. The pupils are irregular, unequal, do not react to light, and are typically Argyll Robertson. The eye-grounds show slight sclerotic changes. The reflexes are present and the knee-jerks exaggerated. His memory for recent events is not as good as it was some years ago.

There is a feeling of well being, and the patient does not seem to be worried about his condition. During the past month there has been striking improvement. The seizures have not returned. The patient does his work without difficulty. The neurologic signs, including the Argyll Robertson pupils, remain unchanged.

Comment.—These cases are important not only because of the close clinical resemblance to paresis but also on account of the extensive neuropathologic study which is offered, at least tentatively, as a prototype for many instances of paresis sine syphilis in which neither toxic agents like alcohol nor lead or a neurologic entity like multiple sclerosis, frontal lobe disease, or encephalitis can be implicated.

Finally, the proposition is advanced that, in view of the accuracy of the serologic findings, including the gold chlorid reaction, an error in the diagnosis of paresis is no longer permissible.

At the Pennsylvania Hospital over a period of many years paresis has never been discovered at necropsy in which the serology was negative during life. Wilson and Winkleman, working with the large material at the Philadelphia Hospital, have not been able to find postmortem paresis in the face of a negative serology. It should be emphasized that there is no typical paretic psychosis. While it is true that a grandiose delusional content and sometimes a depressive trend with somatic delusions are fairly constant, yet manic forms are not infrequent and, in fact, any psychotic entity may be mimicked. If I were permitted to write a diagnostic formula for paresis I should weight it as follows:

Serology	Neurologic signs	Mental symptoms
85	10	5

Finally, it should be added that *if the serology is consistently negative, then the diagnosis of paresis is, in all likelihood, an error.*

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CLINIC OF DR. RICHARD A. KERN

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SOME CAUSES OF FAILURES IN HAY-FEVER TREATMENT[1]

THERE are over 1,000,000 hay-fever sufferers in the United States. The majority of these have their symptoms restricted to a particular pollen season, some time between May and October, and will soon seek, or have already sought, medical advice and treatment. Some will consult physicians who have made an intensive study of this disease, but the majority will be treated by internists and general practitioners. A discussion of some of the causes of therapeutic failures would, therefore, seem timely.

Only some of the causes of failure, for of many, probably, we are still ignorant. Others are beyond our control, such as seasonal variations in the pollen crop; so that a patient who can be brought to a certain state of pollen tolerance, sufficient to protect him in an ordinary pollen season, may in another year, with the same treatment, have marked symptoms when weather and wind conditions combine to expose him to unusually large amounts of pollen. Comparatively few physicians prepare and standardize their own materials for treatment; most of us are dependent on the commercial houses for the preparation of pollen extracts. Several years ago many treatment failures were undoubtedly due to commercial pollen extracts that were of low potency to begin with, or that completely deteriorated in a very few weeks. Happily, this is not true today; but we are still ignorant of the exact nature of the active substance in pollen extracts; therefore there is no absolute standard for determining

[1] From the Medical Division of the Hospital of the University of Pennsylvania.

their potency. Until there is such a standard and until we know the factors that bring about deterioration of pollen preparations, until then will the treatment material itself be a possible cause for treatment failure.

A prerequisite for successful treatment is correct diagnosis. We must have a complete knowledge of the pollens to which our patients are exposed before we can subject them to adequate diagnostic skin tests. It would be futile to test a resident of Pennsylvania with sage brush—that is obvious, but it is equally futile to test with corn pollen a patient whose early summer hay-fever season is spent wholly within Philadelphia city limits and nowhere near a corn-field. On the other hand, that same patient may work daily in a rose garden, and while he may be sensitive to grass as well, grass treatment alone would be inadequate were we to overlook a possible sensitivity to rose pollen, uncommon as this latter condition may be. Few of us are skilled botanists, and we must depend on others for careful botanical surveys. Much has been accomplished in this direction in recent years, and the results are available in the literature, but much work remains to be done. Take, for instance, the case of plantain—a few years ago it was unheard of as a cause of hay-fever in this part of the country, yet we know that from 5 to 10 per cent. of early summer cases give positive skin tests with plantain, and in many of these plantain plays a definite etiologic rôle.

An accurate clinical history is essential—hackneyed expression, but ever timely. Whenever a history deviates from what is typical for any pollen season, we should be on our guard. For example, goldenrod, while it often enough gives positive skin tests, rarely is of clinical importance. Most autumnal hay-fever cases with us stop promptly in early October with the first severe frost which kills the ragweed, while goldenrod blooms merrily on till snow flies, but an occasional case of autumnal hay-fever continues after the first October frost, and lasts until November, and ragweed cannot be responsible for this. In 4 such cases I have found strong goldenrod reactions, and in 2 of these the use of goldenrod as well as ragweed pollen in treatment gave a better result than did ragweed alone.

In the investigation of hay-fever patients we often lose sight of the fact that they belong to that larger group of hypersensitive individuals among whom multiple sensitization is the rule rather than the exception. The majority give a positive family history of asthma, urticaria, and other forms of allergic disease as well as hay-fever. Not a few of them will tell us that they get a rash from strawberries or shell-fish, or that they had eczema in infancy. It is not sufficient, therefore, to test them only with pollens, but we must also include other inhaled substances to which they might be exposed, notably animal epidermal substances, such as feathers and hair; also cottonseed, orris root, and house dust.

The question might be put: If a hay-fever patient is sensitive also to goose feathers, why does he have symptoms only in the pollen season? Why do his symptoms not continue throughout the year? The answer is not certain, but this seems a plausible explanation: A patient may be strongly sensitive to ragweed and only very slightly so to goose feathers. The feather sensitivity is so slight that his mucous membrane in a normal state is not vulnerable, but only becomes so when markedly congested, inflamed, and, therefore, more permeable as a result of the more intense pollinosis. Consequently, in the pollen season the feather sensitivity may succeed in aggravating the disease, and, if unrecognized, bring about the failure of pollen treatment. Moreover, such patients, if carefully questioned, will at times give a history of an unusual amount of sneezing at other times of the year when they happen to catch a cold. Here nasal infection renders the mucosa more vulnerable, just as did the pollen in its season.

Certain it is that such cases exist. Mrs. J. C. gave a history of typical autumnal hay-fever. Skin tests for ragweed were strongly positive, yet in two seasons treatment with ragweed extracts was practically a failure. She was then tested for other inhalents as well as pollens, and a definite reaction to goose feather was obtained. Last year ragweed treatment plus the avoidance of feather pillows gave complete relief. Since then she has noticed that at other seasons of the year if she happens

to sleep on feather pillows when away from home she will sneeze a few times at night or in the morning.

House dust may act in a similar way. Mr. R. P. suffered from typical autumnal hay-fever complicated with asthma. He was first examined in another city and found sensitive to ragweed. Feathers and stock dust extracts reacted negatively. Treatment with ragweed in three successive seasons gave no relief. He then consulted me. My findings were exactly the same: positive reactions to the ragweeds and negative to stock house dusts. An extract was then prepared from his own house dust and it gave a strongly positive skin test. Treatment with ragweed and his own house dust extract gave complete relief in the last three years. Incidentally, this same dust extract has been used in testing other dust-sensitive patients, and only rarely has it given a positive reaction.

While some of the patients may give positive skin reactions to food proteins, and some observers have claimed that such foods play a part in the production of symptoms in the pollen season, the writer has seen no such cases. It is, however, a conceivable possibility and should be kept in mind.

In the treatment of hay-fever, as in that of other forms of hypersensitiveness, the same fundamental rule holds good, namely that avoidance of the offending substance gives better results than do active attempts at hyposensitization. Years ago the hay-fever sufferer's only relief was to be sought in flight from the region where his enemy flourished. Ragweed being limited in its distribution to the continental United States, the autumnal cases found relief by going to Canada or northern Vermont, New Hampshire, and Maine, or to the islands off the northeast coast, and this annual hay-fever pilgrimage still continues. I know of a physician who looks on his hay-fever as a blessing since it gives him a valid excuse for the annual six weeks' vacation which he has taken for nearly thirty years! The grass cases find no such ready refuge, for grass occurs everywhere. Yet one of my patients, an intense sufferer from hay-asthma, for years worked hard every winter that when pollen time came she might take a round trip sea voyage to Australia.

Of course, such complete avoidance is, for practical purposes, not to be thought of. Yet patients can do much to lessen the amount of pollen exposure to which they are subjected. They should be cautioned against trips to the country during the pollen season, and be advised to keep to the center of the city as much as possible. Bedroom windows are to be kept closed during the daytime on clear days when the air is highly charged with pollen. Screening windows at night with cloth, the bottom of which hangs in a vessel with water, has been found useful. Of great importance is attention to keeping down grass or weeds on empty lots near the patient's home. Some ragweed in the yard of a neighboring vacant house was apparently enough to precipitate symptoms in a patient who in a previous season had done well under treatment. If patients take their summer holiday during the pollen season, they should avoid country resorts or motor trips that would expose them to a great excess of pollen, but should chose sea- or lakeside places, for obviously at the seashore the pollen-bearing area is reduced one-half. These measures for a partial reduction in pollen exposure may prove the deciding factors between successful treatment and complete failure, for it seems to be true that the precipitation of symptoms by a transient overexposure to pollen breaks down in a considerable measure the partial immunity which treatment has conferred.

Prophylactic treatment, that is, treatment carried out before the pollen season, is generally agreed to give better results than does treatment given during the period of symptoms, the so-called phylactic treatment. The consensus of opinion is that prophylactic treatment is most successful when carried out over a period of eight to twelve weeks prior to the pollen season. In this way it is possible by gradually increased doses given at five-day intervals to bring the patient to tolerate a very high pollen dosage by the time the season is at hand. Many men would, therefore, attribute treatment failure in certain cases to too late a start. However, Duke, in his recent book, has claimed his best therapeutic results from a short intensive course of injections, at first twice a day, then daily or at longer intervals, depending on reactions, during a period of four weeks or less

before the season. There is as yet no general confirmation of this work. The writer feels that a higher degree of tolerance can be achieved by the prolonged prophylactic method. The woman who used to make the sea voyage to Australia for relief is a case in point; previous attempts at preseasonal treatment over six weeks' time had failed for several years because comparatively small doses would precipitate severe general reactions, so that by the beginning of the pollen season wholly inadequate dosage had been given. In one year, when she delayed her sailing date somewhat, she had to be carried on board the ship on a stretcher. In the last two years treatment was started nearly four months before the pollen season, and by very cautiously increasing the doses it was possible to give very large doses of pollen near the end of the treatment, with practically complete relief from asthma and so little hay-fever that she lost no time at her usual occupation.

Frequently, however, prophylactic treatment is not sufficient to confer adequate protection. In such cases relative fail ures can often be turned into tolerable successes by phylactic treatment. This must be given cautiously, care being taken to avoid overdosage. It is to be remembered that, in addition to the known amount given in the injection, the patient is also receiving an unknown quantity of pollen in the inspired air, and general reactions with their attendant disagreeable symptoms (at times severe hay-fever or asthma for several days) can be precipitated by much smaller doses than is the case in the preseasonal treatment. The usual interval between doses in phylactic treatment is three or four days.

The selection of pollens to be used in treatment must receive careful attention. Obviously, a patient should not be given injections of a pollen to which he is not exposed, even though he might have reacted strongly to it in testing. Many patients are sensitive to several pollens that are closely related biologically: for example, grass-sensitive individuals will react positively to the pollen of half a dozen different grasses. It was early found that injections with one pollen such as timothy, conferred protection not only against timothy, but against the other

grasses as well. Many men, therefore, recommended, and still recommend, the use of timothy pollen alone in the treatment of all grass sensitization. There is, however, increasing evidence to show that collateral protection against related pollens by treatment with only a single pollen is not as satisfactory as when the specific pollens in question are also used. It has been the writer's experience that the use of a mixture of the grass pollens prevalent in a neighborhood yields better results than when timothy alone is given. There is a reasonable basis for this: in rural districts in this part of the country it is quite probable that timothy pollen preponderates greatly over all others, but within suburban and city limits four or five other grasses are present in greater proportions than is timothy. Similarly, a mixture of short and giant ragweed pollens has given better results in the writer's hands than did short ragweed alone. Some patients give a very much stronger reaction to a single pollen than to other related pollens and if there is exposure to that pollen it should be selected for treatment purposes; one patient while mildly reactive to all the grasses was intensely sensitive to June grass. Treatment with June grass alone was adequate for a good result.

Improper dosage, more specifically, inadequate dosage, is perhaps the most important single cause for failure in the hands of the average practitioner. The reason for this is that he treats all his patients alike in that he follows exactly the dosage as outlined by the commercial houses for their treatment sets. What are we trying to accomplish in our treatment? We are trying to bring about in our patient a relative tolerance to the substance to which he is sensitive by subjecting him to increasing doses of that particular substance. The optimal dose, theoretically, at any given time should be the maximal dose that he can tolerate, the dose which will fall just short of producing symptoms. Now there is a wide difference in the degree to which different individuals are sensitive; obviously, a single rubber-stamp schedule of doses will not fit them all. Whatever else may be said of the doses recommended by the commercial houses, they are calculated to be safe doses, safe in the hands of

the inexperienced. Since they are attuned to the level of the very sensitive patients, it is clear that they will be inadequate for all the less sensitive individuals. Much valuable time is therefore lost in the early part of such a course of treatment when the doses are far too small. It is then usually necessary to "revise upward" the dosage recommended in treatment sets.

But some pollen extract makers go further than recommending a certain dose schedule; they actually put out the material in a number of fixed doses, so that the only possible change is a "revision downward." Such sets are to be flatly condemned. Moreover, they leave no material for possible phylactic treatment should it prove necessary. Occasionally treatment sets have gone to the other extreme: a whole course of treatment condensed into four or five doses, each containing a considerable amount of pollen. Here one incurs the possible risk of an excessive overdose that might have disastrous results.

The determination of the proper dose in a given case is not so easy, and certain precautions must be observed. Beginning with a very small dose that will not produce a general reaction (a dilution that just fails to produce a skin reaction), the dose is doubled at each injection. When a given dose produced a slight reaction at the site of injection, or possibly even a very slight transient general reaction, that dose was the maximal and ideal one for that time. The next dose should then be increased by only one-half. Reactions tend to occur on shifting from one pollen dilution to another of higher concentration. It is, therefore, inadvisable to increase the dose at all when changing to a stronger solution. In attempting to reach a dose just short of an overdose we skate on thin ice, and they who skate on thin ice occasionally break through. Patients should, therefore, wait in the office for a time after receiving an injection so that in case a severe reaction develops a hypodermic of adrenalin may be given promptly and repeated in five minutes if there is no relief.

The importance of sensitization to other inhaled substances, such as feathers, hair, and dust, complicating a pollinosis, has been referred to. Treatment in these cases usually means

avoidance of the particular substance. In the dust-sensitive patients, however, injections of a suitable dust extract should supplement the pollen treatment. Horsehair cases must occasionally also be treated in this manner.

Failure to recognize gross intranasal pathologic conditions may determine a therapeutic failure. Of particular importance are nasal polyps, badly infected sinuses, and hypertrophied turbinates that impinge on the nasal septum. A clinical examination by a competent rhinologist should always be supplemented by Roentgen-ray investigation of the sinuses. When sinus infection is present, especially if it has been of long standing, an autogenous vaccine should be prepared and used in treatment. The writer has, however, not been able to demonstrate in such cases any apparent sensitization to the bacterial protein.

Corrective nasal operations on these patients should never be undertaken during the hay-fever season, but always at least a month earlier, so that the mucosa shall have completely healed. In this connection the writer wishes to call attention to a possible factor in the etiology of hay-fever. Not a few hay-fever sufferers date the onset of their disease to a corrective nasal operation performed during a pollen season. Now it is probably true that these patients were pollen sensitive before the operation, that is, their skin would have reacted positively. So we have all seen occasional patients with grass hay-fever and no autumnal symptoms, yet with positive skin reactions to ragweed as well as to grasses. It seems reasonable to suppose that in such moderately sensitive patients without symptoms a nasal operation in the pollen season breaks down the patient's partial immunity by way of the physical breach in his nasal mucosa, and the patient's relative protection once lessened in this way is not regained. There has been a sudden abrupt shift in the balance between a moderately sensitive patient's resistance to pollen absorption and pollen exposure by a lowering of the former, with, as a result, the production of symptoms. Another type of such a shift is probably offered by the patients who first develop hay-fever after overexposure to pollen (for instance, a walk through fields on a dry, hot day). If this

supposition is correct, then no one with a positive family history of allergy should submit himself to an elective nasal operation during a pollen season. Since hypersensitiveness is present in possibly 10 per cent. of the white population of the country, this matter assumes no inconsiderable importance.

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A CONSIDERATION OF SALVARSAN POISONING: ACUTE SIMULTANEOUS POISONING BY ARSENIC AND ALCOHOL COMPLICATING A CASE DIAGNOSED CEREBRAL SYPHILIS

THE fact that innumerable injections of salvarsan, neosalvarsan, and allied arsenical preparations are given without untoward results shows that the arsenic in these compounds is not, as a rule, poisonous. According to Fraser and Duncan,[1] the chance of death after an injection of salvarsan is 1 in 13,000; after sodium salvarsan, 1 in 20,000; after neosalvarsan, 1 in 162,000. The question, then, as Wechselmann[2] points out is, not whether salvarsan is poisonous, but under what conditions it is toxic. In the customary dosage it is atoxic, but its prolonged circulation in the blood, resulting from delayed elimination due to prior infections or diseases, or to other causes, may change the arsenic into arsenic oxid, which is toxic. In this form the arsenic affects the capillary endothelium and interferes with the resistance of the capillary walls to the passage of fluids. This explains why exanthemata and symptoms referable to the central nervous system are observed in the course of salvarsan treatment.

The effects of injections of these arsenical preparations are usually classified as immediate and late. The immediate effects consist in a group of vasomotor symptoms which have been designated the "nitroid crisis." With the onset of this reaction the veins of the neck suddenly become engorged, the face red, the conjunctiva injected, with swelling of the face and lips. This reaction may progress to syncope and death. Other symptoms accompanying this reaction are pain in the teeth and gums and a peculiar taste in the mouth. There may also be rigor, headache, and a rise of temperature. These usually come within two

hours after the injection and pass off the following day. There may be vomiting, diarrhea and herpes labialis, and skin eruptions, such as urticaria, macular, papular, follicular, polymorphic, or erythematous manifestations (Fraser and Duncan). Edema may occur, and edema of the optic disks is often seen during the course of a dermatitis. Other symptoms may be coryza, hepatic tenderness, and hypersalivation.

At times within twenty-four to thirty-six hours after an injection of salvarsan there appear affections of one or more of the cranial nerves, the third, sixth, and eighth being most frequently involved. There may be such symptoms as paresis of certain eye muscles, inequality of the pupils, vertigo, labyrinthine deafness, sluggish reflexes, and cardiovascular changes. Milian,[3] writing in 1924, states that these symptoms were formerly attributed to the toxic action of the drug, but conclusive proof of their syphilitic origin is found in the fact that they disappear promptly when treatment with 606 or 614 is resumed.

Certain phases of salvarsan poisoning are of special interest in connection with the following case, and will be discussed after the details of this case have been described.

Case Report.—D. C., a Lithuanian, aged thirty-two years, a waiter, was admitted to the Philadelphia General Hospital, service of Dr. Joseph Sailer, with the diagnosis of lues. He had been well until a week previously, when he had received a third injection of salvarsan. The needle missed the vein and the arm became tremendously swollen; swelling of the face, legs, and other arm soon followed. On the day of admission the patient became totally blind and his hearing was greatly impaired.

Physical examination showed a well-developed and well-nourished man. He appeared to be acutely ill and in some pain; his face wore an expression of anxiety. There was some edema under the eyes and moderate edema of the feet and legs. The left arm and forearm, near the elbow, were much discolored, swollen, hard, and indurated. The foreskin and scrotum were edematous. There were two recent scars on the foreskin. The shoulders, upper chest, and back were covered with a brownish macular eruption, irregular in form.

Examination of the nervous system revealed no abnormalities with the exception of the seventh and eighth nerves. At this time the patient's symptoms were regarded as due to arsenic poisoning, and the prognosis was considered very poor, both for life and for the recovery of sight. Forced fluids, alkalis, and potassium iodid were advised. The temperature was about 99.5° F., the pulse was 85, and the respiration 23.

The urine was yellow in color, alkaline in reaction, and had a specific gravity of 1018; it contained a great deal of albumin, many red blood-cells, a few leukocytes, and an occasional hyaline cast. It was negative for sugar.

The diagnosis was optic neuritis, acute nephritis, and syphilis.

The day after admission the patient had two convulsions involving apparently all the voluntary muscles; they lasted from two to four minutes, during which there was almost complete cessation of respiration and extreme cyanosis. The first convulsion was allowed to go to its natural termination, which was reached in about half an hour. The other convulsions were controlled by giving morphin.

Dr. Stokes, who saw the patient in consultation at this time, thought the case might be one of salvarsan poisoning, but probably was one of cerebrospinal syphilis. He advised the giving of sodium thiosulphate, but thought it best to wait a day or two before giving the drug.

The blood-count showed red blood-cells, 3,280,000; leukocytes, 32,000; polymorphonuclears, 60 per cent.; lymphocytes, 21 per cent.; mononuclears, 11 per cent.; basophils, 1 per cent. The blood-sugar was 119, urea 14, uric acid 4, and creatinin 2. The Wassermann reaction was 2 plus with the cholesterin antigen and negative with the Noguchi antigen; the spinal fluid Wassermann was 4 plus with both antigens. There were 16 cells per cubic centimeter, a trace of globulin, and a slight trace of arsenic.

On the second day the patient's condition became more critical; he was cyanotic and there was extreme rigidity of the neck. The patellar reflexes could not be elicited. It was the writer's impression that the patient was suffering from an acute toxemia, probably due to syphilis, arsenic or methyl alcohol, with acute nephritis. It was learned through friends of the patient that he had been drinking very heavily. This made the diagnosis of wood alcohol poisoning seem quite probable.

The patient continued to have convulsions, with definite signs of cerebral irritation, and grew progressively weaker. The Kernig and Brudzinski were positive, and the Babinski was suggestive. The temperature was about 99.5° F., the pulse 80. The prognosis was very poor. On the third day after admission the patient began to improve, and on the fourth day his condition was markedly changed for the better. The blood-sugar was 130, the blood urea 40, and uric acid 6. The pulse rose to 110; the temperature was 98.5° F. By the sixth day the patient's sight and hearing were apparently normal. He became more rational and took food and medication well. By the seventh day the urine showed merely a trace of albumin, an occasional granular cast, and a little mucus; the leukocytes numbered 20 to 30 per field. For several days he complained of headache, which was severe and continuous.

A blood-count on the twelfth day after admission showed red cells, 4,900,000; white cells, 18,200; hemoglobin, 80 per cent.; mononuclears, 2 per cent.

Because of the continuous headache, which was described as a dull, aching pain throughout the entire head, an ophthalmologic examination was made. The eyes were reported to be perfectly normal. The cerebrospinal fluid was perfectly clear and under moderately increased pressure. The lumbar puncture produced no effect whatever on the headache. Examination at this time suggested that the patient might be in the early stages of paresis.

Before his discharge the patient, from whom it was impossible to obtain any history at the time of his admission, stated that he had been receiving antisyphilitic treatment (the first course) at another hospital. Salvarsan or neosalvarsan had been administered once a week, on Fridays, and in the interval between injections he was receiving mercury by inunction and potassium iodid by mouth. Six days before admission he noticed a swelling of his hands, face, feet, and scrotum. The swelling slowly increased, and five days later, when he went to the dispensary, he called the physician's attention to the edema, and was told to stop the mercury inunctions, but the usual dose of salvarsan was administered. In making the injection the doctor missed the vein and injected the drug into the arm, continuing the injection in spite of the patient's pain and protests. The arm became greatly swollen and excruciatingly painful. On the following day the generalized edema was more marked and there was severe headache and vertigo. On the second day after the injection, the day on which he was admitted to the hospital, he noticed on rising that vision was blurred and the vertigo more marked. Suddenly, a short time afterward, he lost his sight completely, and to a great extent his bearings also. He scarcely remembered coming to the hospital, and recalled nothing after his arrival there.

He had had no previous illness of any account, except a bilateral hernia in 1918, a chancre in 1919, and gonorrhea in 1920. He drank moderately before prohibition, and heavily since then, always taking whisky. For two months prior to admission he had been drinking more heavily than usual, but he had stopped altogether two weeks before entering the hospital, owing to the fact that liquor made him sick, causing headache, nervousness, and insomnia. About three months before his present illness he had had delirium tremens, but started drinking again as soon as he was over the attack. His family history was negative.

After a stay of twenty days in the hospital the patient had fully recovered. He was instructed to return to the dispensary for further treatment of his syphilis by mercury and the iodids (not by salvarsan). He was examined by Dr. McConnell, who expressed the opinion that the symptoms might be explained on the following basis: The alcohol poisoning subsided two weeks before admission, when the patient stopped taking alcohol; its effects, however, were re-established by the additional element of arsenic, which was responsible for the acute nephritis. This had cleared up entirely at the time of the patient's discharge.

The final diagnosis was: (1) Cerebral syphilis; (2) acute nephritis (arsenical); (3) acute encephalitis (arsenic, syphilis, alcohol); (4) chronic alcoholism.

Discussion.—The part played by the various factors that might have exerted an influence in the production of the symptoms in this case cannot perhaps be definitely appraised. It is probable that the impaired condition of the patient's organism due to chronic alcoholism constituted the basis which made him fall easy prey to the effects of arsenic, but it is also possible that

cerebral syphilis participated in the etiology of the cerebral symptoms.

The outstanding fact for consideration is that salvarsan or neosalvarsan was administered to an alcoholic patient. In a summary of the literature with reference to the reactions following the injection of arsenobenzol preparations Fraser and Duncan list as relative contraindications to the use of these drugs chronic nephritis, hypersusceptibility to arsenic, early cardiovascular changes, hemophilia, hepatic disease, alcoholism, and lymphatism. They emphasize that alcoholics are usually more susceptible than others, and that this is due to the diseased condition of the renal vessels. A sufficient number of cases has been reported in which alcoholic patients have developed serious symptoms following salvarsan injection to at least serve as a warning that all such patients in whom this treatment is attempted should be carefully watched for the development of untoward symptoms. Illustrative of this class of cases is one recently reported by Fritz[4]: A man aged thirty-one, after a second dose of 0.9 gm. of neosalvarsan, given one week after the first, indulged in alcoholic and sexual excesses. His temperature rose; he had tonic and clonic convulsions, and loss of consciousness, in which he died. Autopsy revealed the typical picture of hemorrhagic encephalitis. In commenting on this case Fritz says, "As the man had been an alcoholic, and his capillaries were probably injured, it is likely that there was a combined action of alcohol and salvarsan." Likewise in the author's case it may be assumed that the alcoholism established conditions in the capillaries which interfered with the proper elimination of the salvarsan and induced an exaggerated susceptibility to arsenic.

According to the report of the British Research Council,[5] which was empowered to make an exhaustive study of the toxic effects of arsenobenzol preparations, it was found that the ill-effects which may end fatally are encephalitis hæmorrhagica, acute yellow atrophy of the liver, exfoliative dermatoses, and their complications. Encephalitis usually occurs within two or three days after an injection, most frequently after the second injection of the series. Certain other effects, rarely encountered,

but which may end fatally, are active renal damage, ulcerative enteritis, polyneuritis, and aplastic anemia. In the case herein reported the symptoms of edema and cerebral irritation, with involvement of the ocular and auditory nerves, and also the dermatosis, give a remarkably typical picture of salvarsan poisoning. If Wechselmann's explanation of the action of arsenic oxid upon the capillaries is correct, it is evident that this effect must involve the capillaries of the kidneys as well as those of the rest of the organism, and thus the impairment of kidney function would be accounted for. This same writer claims that the simultaneous administration of mercury and salvarsan seriously affects elimination, as excretion of the former makes unusual demands on the kidneys. It is thus easy to see that in the case under consideration, in which mercury inunctions had been combined with salvarsan, an increased burden was placed on the kidneys, whose efficiency was already lowered by chronic alcoholism.

The macular eruption, which was present in this case, is explained by the capillary injury and consequent capillary permeability, which are responsible for defective elimination of the arsenic circulating in the blood-vessels.

Another point of interest is that the last salvarsan injection preceding the development of toxic symptoms, either through accident or carelessness, was given intramuscularly. Beinhauer[6] says that of the early accidents associated with the administration of salvarsan, the commonest is the infiltration of the tissues, owing to the needle not being properly inserted. *When this happens the needle should be withdrawn immediately.* In the case under consideration this advice was not heeded. Just how this error in technic influenced the development of symptoms is problematic. M. Pomaret[7] has shown that acid intravenous injections, though colloidoclastic and hypotensive in their effect, if given subcutaneously or intramuscularly, produce no cardiovascular action sufficiently marked to be recorded graphically. He found that intramuscular injections of the arsenical compounds avoided the nitroid crisis and secured, with a minimum of noxious effects, a maximum therapeutic activity, because elimination is effected more slowly after the intramuscular

injection than after the intravenous. With this finding in mind, it might be suggested that in this case the impaired eliminative capacity of the patient which was already present, together with the slower excretion of the salvarsan administered intramuscularly, may have resulted in a cumulative action of the drug, or may have caused its retention until its form was changed to that of arsenic oxid, which is extremely toxic.

It is, however, particularly around the encephalitis and eye symptoms in this case that interest centers. Hemorrhagic encephalitis is readily explained by capillary permeability to the serum, which results in edema, swelling of the brain, diapedesis of erythrocytes, and purpura cerebri. According to Wechselmann, none of these symptoms are due to neurotropism on the part of the arsenobenzols. Vorthenberg[8] reports a case which serves to illustrate the manifestations of encephalitis after the injection of salvarsan. A man, receiving a third course of treatment with silver salvarsan, took a bicycle ride instead of the prescribed bed rest. The reaction was characterized by fever, pain in the eyes and head, disorientation, eleptiform attacks with unconsciousness, cyanosis, Cheyne-Stokes' breathing, accelerated and irregular pulse, vomiting, loss of control of the bladder and rectum, and tonic and clonic spasms. The corneal and pupillary reflexes were absent; the tendon reflexes were weak. A cure, brought about in two weeks by daily injections of suprarenin, was attributed to the fact that suprarenin restores the elasticity of the arteries, and thereby avoids cerebral hemorrhages.

In a case reported by Woencklaus,[9] after the administration of 4.35 gm. (*in toto*) of neosalvarsan during a period of four weeks, severe encephalitis developed and death ensued. At autopsy the brain was found to be red and swollen. The lateral ventricle was dilated and filled with clear fluid. Numerous hemorrhagic points were seen in the brain substance, especially in the region of the posterior horn of the left ventricle. These are the typical findings when arsenic poisoning takes the form of hemorrhagic encephalitis.

The involvement of the ocular and auditory nerves is of special interest because of the vast amount of discussion as to

whether this involvement is due to the injection of salvarsan or to the effect of the syphilitic virus upon the brain and nerves. Soon after salvarsan began to be used therapeutically (1909) investigations were undertaken to determine whether it produced any severe organotropic results. In the course of the next two years Finger,[10] Blaschko, Held, Oppenheim, von Zumbusch, and Fordyce had reported cases which suggested that salvarsan had a deleterious effect on the optic and auditory nerves (Corbus[11]). Benario[12] in 1911 collected reports of all the cases of central nerve involvement, there being 126 single observations in 14,000 treated cases. This author's findings agreed with those of Ehrlich's animal experiments, namely, that salvarsan does not exert injurious effects on the optic nerve as do atoxyl and the related preparations of arsenic.

Hoppe's investigations, cited by Steindorff,[13] show that salvarsan has only a slight chemical affinity for nerve tissue; three days after injection he could find no arsenic in the brain, spinal cord, or optic nerve. In his report on 700 cases Steindorff found that blindness referable exclusively to salvarsan has not so far been definitely determined, but, on the contrary, the remedy has a favorable effect in primary and tertiary affections of the eyelids and conjunctivæ, in dacryocystitis, scleritis, gumma corneæ, and in luetic disease of the orbital bones. Affections of the retina and choroid are frequently favorably influenced.

Crisp,[14] commenting on Benario's report, concludes that these symptoms (ocular and auditory) are not manifestations of salvarsan poisoning, but that they arise from isolated groups of spirochetes persisting in these protected regions after the sterilization of the general mass of organisms. Geronne and Gutmann[15] find that in disturbances of these nerves the process is very similar to that affecting the meninges. They cite 3 cases of involvement of the meninges, in 2 of which there was paralysis of both facial nerves, and in the third paralysis of the seventh and eighth nerves. They also mention 2 cases of optic neuritis, in 1 of which there was the Ménière symptom complex.

Heath[16] in 1912 confirmed these statements, and observes that the lesions are inflammatory, as in syphilis, not degenera-

tive, as after atoxyl, and that they are usually temporary in duration, as argued by deSchweinitz, Sheelp, Weinfeld, Hirschfelder, Montgomery, and Blaschko. He also points out that they are seen after small doses of the arsenobenzols, while large doses are used with no ill-effects. He argues further that these symptoms are never encountered in non-syphilitic diseases treated with salvarsan. Replies to a questionnaire sent to syphilologists and ophthalmologists in Indianapolis revealed no ill-effects after salvarsan except 1 case of temporary photophobia and 1 case of choked disk, appearing several months after the injection, and in which recovery took place under mercury and the iodids.

Casey Wood, in his System of Ophthalmology, mentions a case reported by McNeil, Robb, and Moll,[17] in which they consider that optic atrophy resulted from the administration of salvarsan intravenously during the second stage of syphilis, the dose being 0.6 mg. He also states that Wernicke[18] reported 10 cases of optic neuritis or neuroretinitis after injections of salvarsan, of which 9 were likely due to the drug, or were not prevented by it. After reporting several other instances of late lesions, Wood says, "Salvarsan possesses the property when given in sufficient amounts of provoking more or less severe affections of the special nerves, either through direct action on the syphilitic virus or through indirect action on the body tissue. There is no ground for the belief that salvarsan causes atrophy of the optic nerve through a direct toxic effect." Likewise W. C. Souter[19] states that there is no evidence of any direct eye reaction after the injection of salvarsan, basing this conclusion upon his experience with 500 injections.

Since the technic of the administration of the arsenobenzols has been perfected serious reactions following the administration of ordinary doses of these preparations are being reported less frequently. However, during the past few years the question under discussion has again been brought to the front. R. Arganaraz[20] (1915) describes 28 cases of grave toxic lesions of the uveal tract and the sensory cranial nerves following the therapeutic use of arsenobenzol. He declares that in patients at-

tacked by optic neuritis the use of salvarsan is contraindicated. Recently Milian[21] reported 2 cases in which the injection of neoarsphenamin caused a transient myopia. The phenomenon appeared in ten to thirty-eight hours after the injection and persisted for two days. According to this writer the myopia may be due to toxic paralysis of the sympathetic nerves. He has noted this complication only four times in fourteen years. The visual disorders were preceded by a violent febrile reaction, headache, and muscular pains, with or without nitroid crisis. It is Milian's opinion that the localizing factor is first and foremost a pre-existing lesion of some portion of the sympathetic nervous system. He points out that whereas drugs of the arsenobenzol group have an affinity for the sympathetic system, the oxygen compounds of arsenic have an affinity for the motor nerves, and phenylarsenic compounds (such as atoxyl) for the sensory, optic, and auditory nerves.

A report by S. Weiss,[22] covering the past ten years' experience with salvarsan at Bellevue Hospital, shows that there were 34 patients who suffered from more or less severe, mostly acute, toxic effects of arsphenamin. There are recorded in the office of the Chief Medical Examiner of New York City 29 fatalities occurring during the past six years, in which the relationship between the injection of arsphenamin and death is definite. In neither of these groups of cases is any reference made to eye symptoms. In a number of cases, however, there is reference to injuries to the cardiovascular system and the kidneys. In connection with the kidney condition the statement of Raiziss and Brown[23] is of interest. They believe that many of the reactions noted may be secondary to injuries sustained by the kidneys, and hence, before giving the drug, renal function should be carefully tested.

With reference to the use of sodium thiosulphate in the treatment of arsphenamin encephalitis, Ravant in 1920 published observations showing that this drug is useful in any form of poisoning due to arsenic, mercury, lead, or bismuth. Since that time numerous reports have appeared showing quite remarkable results from the administration of sodium thiosulphate in salvarsan

poisoning. McBride[24] reports the case of a boy aged four years who developed hemorrhagic encephalitis three days after the third injection of sulpharsenamin. He attributes recovery in this case entirely to the use of sodium thiosulphate, for the reason that untreated cases of as great severity previously reported all terminated fatally. Groehl and Myers[25] have studied 75 cases with respect to the arsenic content of the blood, the urine, and scales from the skin at the time of onset of dermatitis or jaundice. In every instance, with the administration of sodium thiosulphate, the arsenic output has been satisfactory, and the case has cleared up in an abnormally short time. In the author's case the use of adrenalin seems to have produced quite as satisfactory results as those attributed to thiosulphate. The administration of the latter drug was considered for a time, but as the patient's condition improved it was not deemed necessary.

While the discussion of this case may not have cleared up effectively all the questions that suggest themselves, it has served to emphasize certain points:

1. Before administering salvarsan a careful history of the patient should be taken to exclude any contraindications to the administration of the arsenobenzols.

2. Tests of kidney function should be carried out, and the condition of the liver should be investigated.

3. The technic of the injection should be performed with the most scrupulous attention to every detail.

4. Arsphenamin should be administered in doses far removed from the danger line.

5. After the administration of salvarsan, or any of the allied arsenicals, patients should be carefully watched for any untoward reaction, and upon the appearance of any symptom indicative of such a reaction the administration of the drug should be discontinued.

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CLINIC OF DR. JAMES E. TALLEY

PRESBYTERIAN HOSPITAL

ANGINA PECTORIS. DEATH, AUTOPSY

WE will discuss a patient whose electrocardiograms you have seen. He had been in the hospital for two months, but for some sixteen months had been suffering from dyspnea and substernal distress. The man was fifty-seven years old, was overweight, and in good health until the attacks of dyspnea and substernal distress began, especially after slight exertion and after meals. During the last year they have increased in frequency and severity. Five months ago his physician found a systolic blood-pressure of 240 and albumin in the urine. For four months preceding death the patient has been confined to his room. Even slight exertion caused much dyspnea and substernal discomfort, but no actual pain that radiated to the arms. After much questioning he did admit that during the attacks the arms sometimes felt numb. He describes the attacks as a smothering feeling at the middle of the breast bone and an inability to catch his breath, rather than actual pain. Ordinarily, the spells last but a few minutes and are relieved by inhalations of amyl nitrite or nitroglycerin. Two weeks before admission, for the first time, he had to have morphin once for relief.

On admission to the hospital the examination showed that he had had attacks of tonsillitis, once with quinsy, up to the age of twenty-three, when the tonsils were removed. There is no history of rheumatic fever or chorea. In spite of the high blood-pressure he had no headache and no vertigo. His appetite was good, and while he was at rest the taking of food did not precipitate the pain. The man sat up in bed by preference. The lips were slightly cyanotic and his expression a little anxious.

The remnants of his tonsils were not healthy looking. The teeth were in but fair condition. The thyroid was not palpable. The lungs were apparently negative. The heart was enlarged, the apex rate was 105 and regular, the sounds were of poor quality and distant, the aortic second sound was accentuated. There was a soft, blowing systolic murmur, not well-transmitted, heard at the apex. Blood-pressure was 185 systolic and 125 diastolic. Radials were equal and synchronous. His arteries were distinctly hardened. There was a marked arcus senilis. The abdomen was full, but there were no enlarged organs and no evidence of fluid was found. There was no edema. Examination of his nervous system was negative. His blood-pressure throughout his stay in the hospital was high, the average systolic was 180 and the average diastolic was about 110. His respirations averaged about 20. For a month at least the evening temperature was from one-fifth to three-fifths above normal and the morning temperature slightly subnormal. This may have been due to the tonsils. At times one thought of the possibility of infarct, but only on one occasion did the leukocytes reach 10,000. His blood was of good quality. On admission the urine showed a few hyaline and light granular casts with a faint trace of albumin, but the specific gravity was 1020. After admission no casts were found, so that evidently the kidneys were suffering only from his general arterial hardening. The blood urea nitrogen was 16 mgm. per 100 c.c. and the Wassermann was negative. Several electrocardiograms were taken; they always showed a regular rhythm with normal conduction and a left preponderance, and TI and TII were flattened. During the spells of substernal distress the pulse rate sometimes ran to 120 or 130, but the electrocardiograms showed it was a simple tachycardia. A polygram showed alternation, but apparently it was not constant. The telroentgenogram was as follows:

12/4/25: Transverse diameter of heart shadow, 13 cm.; right border 4 cm. to the right of center; left border 9 cm. to the left; oblique 15 cm.; vertical 10 cm.; shadow in superior mediastinum, 7 cm. Transverse diameter of the chest 27 cm. Diaphragm and chest generally negative. Fluoroscopic examina-

tion: Apparently movements of heart show no great variation from the normal. Arch possibly slightly dilated, but no distinct sacculation can be seen.

Gastric Analysis.—A fractional test-meal showed a lack of free hydrochloric acid and a reduction in the total acidity. Throughout his two months' stay in the hospital every few days the patient had attacks, but at first they were not very severe.

In the middle of December he had one attack which lasted three hours and was little affected by nitrites and morphin. During this attack the pulse was regular and weak and the apex rate was 155 per minute. Electrocardiograms showed only a simple tachycardia. There was nothing in the electrocardiogram to suggest coronary thrombosis.

Late in January the patient had seven attacks of pain which nitrites failed to relieve as they had before. On the 24th he had six attacks, and on the 25th of January an attack began at 6.30 P. M. His heart sounds and the pulse became rapid and weak and the patient died suddenly at 11.30 P. M.

Clinically the picture was one of cardiovascular sclerosis and hypertension without any important renal element. As the attacks grew longer—lasting on a few occasions as much as three hours and in the final attack five hours—one expected to find some evidence of coronary occlusion, and its absence makes doubly interesting the pathologic report on the heart which we owe to Dr. John Eiman's kindness. The lungs, liver, spleen, and kidneys showed marked chronic passive congestion; otherwise the interest of the postmorten centers upon the heart, and the report as originally made by Dr. Eiman is given in full:

"**Heart.**—Right border extended 4.5 cm. to the right of midline. Left border 11.5 cm. to the left of midline. The area of absolute dulness was increased and measured 10 x 7.5 cm. It weighed 620 grams and measured 18 x 16 x 7.5 cm. There was an excessive amount of subepicardial fat, especially over the right side anteriorly. The tip was blunt. Over the lower half of the left ventricle near the septum there was observed slight unnatural bulging. The myocardium over this area when viewed

through the epicardium was more yellowish in appearance than in other parts. The coronary arteries and the branches were moderately tortuous and the larger branches were quite firm in places, hard, and yellowish white in color. The orifices: Mitral 11.2, aortic 7.5, pulmonic 8, tricuspid 14. Mitral leaflets showed no noteworthy lesions. Aortic leaflets showed a fairly marked diffuse thickening, but no calcareous infiltration. The pulmonary and tricuspid leaflets were negative. The thickness of the left ventricle varied from 7 mm. at the tip to 27 mm. near the auriculoventricular groove. Thickness of the right ventricle varied from 5 to 6 mm. Thickness of the right auricle, 1 to 2 mm., and thickness of the left auricle 2 to 3 mm. There was no evidence of a cardiac aneurysm. The myocardium was firm in consistency and showed rather marked diffuse increase of connective tissue. In the area over the lower part of the anterior surface of the left ventricle there was very extensive connective-tissue replacement of the muscle. All the cavities showed a marked dilatation.

"Before the heart was hardened and opened a cannula was tied in the left coronary artery and mercury was injected under 200 mm. mercury pressure for five minutes. The orifice of the right coronary artery remained open. In about a minute after beginning the injection into the left coronary mercury began to run out from the orifice of the right coronary artery. This indicated that anastomoses existed between the branches of the left and right coronary arteries.

"Roentgenograms were taken. They showed fairly complete injection not only of the larger branches but also of comparatively small branches of both the left and right coronary arteries. The large and medium-sized branches of both coronaries showed very marked and fairly abrupt variations in diameter. The larger branches showed very numerous small fusiform aneurysms. There was nowhere, however, complete occlusion of the larger branches. At the tip of the left ventricle there was an area which was comparatively avascular. This area corresponded with the area showing a marked overgrowth and connective-tissue replacement of the muscle.

"Microscopic examination of the arteries revealed advanced arteriosclerosis with calcareous infiltration here and there. There was also marked diffuse and patchey overgrowth of dense

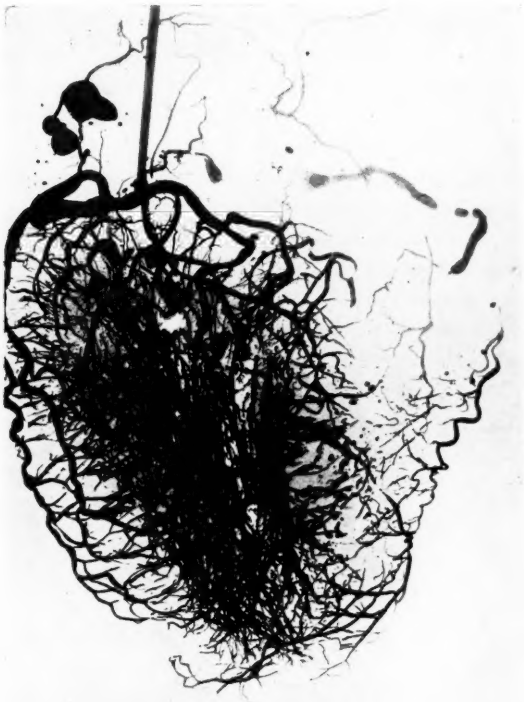

Fig. 6.—Cannula in left coronary artery, right coronary artery open. Mercury injected under 200 mm. pressure into left coronary artery. Note marked variations in diameter and multiple fusiform aneurysms of the larger vessels. No evidence of complete occlusion of lumina of larger vessels. The tip of the left ventricle shows an avascular area where there was extensive connective-tissue replacement of muscle (Dr. John Eiman).

hyalinized connective tissue throughout the myocardium. Sections taken from the fibrous area of the left ventricle showed comparatively few remaining muscle-fibers; the connective-tissue replacement being very extensive.

"**Summary.**—Marked coronary sclerosis with calcareous infiltration and multiple fusiform (arteriosclerotic) aneurysms of the larger branches of both coronary arteries. Extensive coronary sclerosis leading to diffuse and localized, or patchy, sclerosis of the myocardium."

The extreme arterial hardening and the increased severity and length of the attacks of pain would naturally lead one to expect that such a heart would show some coronary branch thrombosis. Dr. Eiman's careful study of the coronary circulation showed that the process was a slower one. On account of faulty circulation the healthy muscle-fibers were slowly but continuously supplanted by connective tissue. A study of the injection of the vessels leads to a better understanding of how the myocardium was robbed of its proper blood-supply and, in this patient, instead of a final thrombosis of a vessel, there were attacks of simple tachycardia which robbed both the heart and brain of its proper blood-supply, and it was during such an attack that the patient succumbed. Furthermore, it is easy to see how the vessels with their lumen so impaired are more easily influenced by spasm.

HYPERTHYROIDISM FOLLOWED BY HYPOTHYROIDISM

THE patient, an artisan, forty years of age, presented himself with the following history: In 1917 he developed symptoms of hyperthyroidism. He was nervous; his pulse was rapid; his eyes were prominent; he lost 10 pounds in weight and his thyroid was slightly enlarged. He began *x*-ray treatment in May, of 1918, and for four weeks he had weekly treatments of four to five minutes' exposure. Later it was made every two weeks, and still later, monthly. At the last treatment he was slightly burned. This burning influenced the hair so that he did not have to shave the lower part of his face for three months. After two months' treatment he began to improve, and by the end of the year he was entirely normal, and remained entirely well and free of symptoms until January, 1925. At this time he noticed that his calf muscles would cramp easily and that his other muscles were somewhat similarly affected. He noticed this especially on rising in the morning. Simply striking a muscle, as the leg, against the chair would cause it to cramp, and at present he has this peculiar myotatic irritability, so that if you grasp his arm at the level of the biceps with your fingers and make pressure, a ring of muscle, $\frac{1}{2}$ inch in height and the width of the finger, will stand up, and then gradually disappear. The same thing is true of the calf muscles. He has noticed that his skin has become dry and that he is tired and listless. He works with difficulty and has spells of drowsiness. At times his arms become numb and tingle from the elbow to the hands, but the fingers never blanch. Formerly he was active in athletics; now he has no interest. Smoking makes him dizzy.

This symptomatology naturally suggests that the thyroid has gone from a state of overactivity to a state of underactivity, and he was admitted to the hospital for study.

History on Admission.—Patient is 5 feet, 5 inches in height; stripped he weighs 120 pounds. His temperature was from nor-

mal to 97° F. His pulse, which was around 60 when first seen, rose to 70 and later to 80. Respirations were 16 to 20.

Patient gave a history of typhoid at the age of eighteen; appendectomy in 1913; severe influenza in 1918, during which he spat blood. His general habits are good. His blood-pressure was 113/54. There is a moderate exophthalmos, slight lagging of the upper lids, and Dalrymple's sign is evidenced. His teeth and tonsils are good. The thyroid is hard to palpate. At the apex of the right lung there is slight roughening of the breathing and there are some râles at both apices. The heart is not enlarged. The rhythm is regular. There are no murmurs, but the sounds are faint and the muscular quality poor. He is of a visceroptotic type. The liver is slightly palpable below the costal margin. There is no edema of the extremities. His nervous examination is negative. A slight tap on a muscle brings out the myotatic irritability spoken of above. *x*-Ray of the chest shows some tenting of the right diaphragm and the hylus shadows are particularly heavy on the right side; the peribronchial thickening in the right middle and upper lobes is marked. There is marked calcification of the cartilages. The conclusions are that this lung shows some fibrosis, but it is not active. The heart is normal in size and position. His frontal sinuses are small, the antri, ethmoids, and anterior ethmoids are clear; the posterior ethmoids and also the right sphenoids appear cloudy. There is no definite infection of the teeth. Two specimens of sputum were negative for tuberculosis. A fractional test-meal showed the absence of free hydrochloric acid and a low total acidity. The electrocardiogram was of small voltage, but otherwise normal. Urine was normal in quantity and quality. The blood urea nitrogen was 10. The Wassermann was negative. The chlorids were 450. The CO_2 59 volumes per cent. The blood calcium 11.5 mgm. per 100 c.c. The blood-sugar control 94; first hour, 154; second hour, 89; third hour, 108. The quality of the blood and the differential count were normal. The average basal metabolism was minus 17 per cent.

This man has been under observation ever since. At first it was supposed that he was suffering from hypothyroidism, and

probably that the parathyroid was involved also; but inasmuch as the blood calcium was normal, he was put simply upon desiccated thyroid gland; at first 2 gr. three times a day gave him substernal distress, but he was able to take 4 gr. with comfort for a time, and more recently he has been taking but 1 gr. three times a day. At first his weight fell off, but it finally reached an equilibrium so that he averaged in his clothes 127 pounds as compared with his weight of 132 pounds when first seen in the office. His pulse rate, which originally was rather slow, is now around 80; his blood-pressure has risen, so that it averages about 125 systolic and 75 diastolic. The muscle phenomena spoken of above is still present, but not so easily elicited, and it does not bother him if he happens to strike his arm or leg. He had many warts on his hands which have disappeared since he has been taking the thyroid. He has lost his listlessness, his somnolence, and his weakness, has regained his appetite, but he has not quite the same surety in his work that he had formerly, and his memory is not as good. He finds that in assembling a piece of machinery he may have to do it sometimes twice and occasionally three times, whereas he used to do it perfectly correct the first time.

We all have seen a number of patients who have refused operation for hyperthyroidism and have been treated medically, combined with *x*-ray; but this is the only one we recollect in which hypothyroidism has followed this treatment. There was never any history of greatly enlarged thyroid in this patient, and there is a possibility that the gland might have reached the atrophic stage without *x*-ray. However, his history has a lesson for us: When he began his improvement after the second month it would have been better to have waited for some distinct sign of retrogression before giving him more *x*-ray treatment. The minute examination of the thyroid is apt to hold many surprises in any case. A small, rounded adenoma, less than 2 cm. in diameter, was recently removed from another patient, and what seemed to be a simple adenoma showed not only adenomatous hyperplasia but also areas of chronic suppurative inflammation.

CLINIC OF DR. ELMER H. FUNK

PENNSYLVANIA HOSPITAL

LOBAR PNEUMONIA. PNEUMOCOCCUS ENDOCARDITIS. CLINICAL HISTORY. LABORATORY STUDIES. NECROPSY. COMMENTS.

W. P., male, aged sixty-five years, was admitted January 20, 1926, with a history of having been ill for eleven days. The onset was characterized by headache, weakness, cough, and feverishness. The cough was dry and only occasionally productive of a scant mucoid expectoration. The day before admission he became suddenly worse, with aggravation of the cough, shortness of breath, and pain on the left side of the abdomen. The physical examination on admission revealed a rather poorly nourished individual who seemed quite ill and mentally dull. There was moderate dyspnea and slight cyanosis. The thoracic expansion was diminished on the left side, especially in the upper part. The percussion note over the left side anteriorly was dull with a tympanitic element. Over the same area intense tubular breathing and many medium râles were audible. In the left axilla and posteriorly the percussion resonance was fairly clear, breath sounds rough, but not tubular, and scattered medium râles were audible. A friction sound was distinctly heard over the left chest anteriorly and in the axilla. The signs of note on the right side were hyperresonance in the right axilla with distinct suppression of the breath sounds. The apex-beat was visible and palpable in the sixth interspace a little outside the left midclavicular line. The heart sounds were clearly heard, although definitely enfeebled. The heart action was regular and no murmurs were audible. The pulse was 108 per minute, regular, and of fair volume. The blood-pressure

was systolic 125, diastolic 75. The abdominal examination revealed some tenderness of the abdominal wall over the left rectus muscle. The tenderness seemed to be in the abdominal wall rather than below. There was, however, no localized redness or swelling. The liver, spleen, and kidneys were not pal-

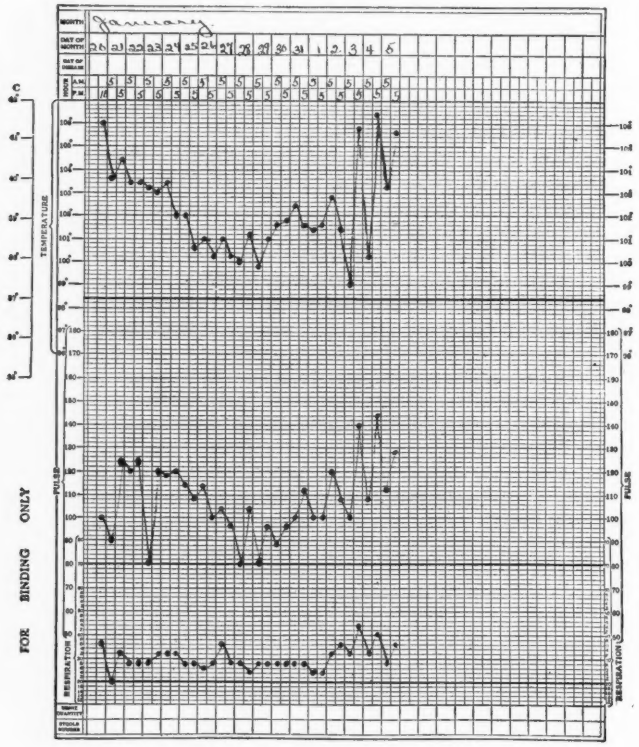

Fig. 7.—Clinical chart.

pable. The examination of the extremities revealed an area of redness and swelling on the dorsum of the right foot. The redness extended to above the ankle-joint. With these findings a definite diagnosis of lobar pneumonia was made, with a tentative assumption of blood-stream infection with metastatic infec-

tion of the right foot. The blood examination revealed 17,500 leukocytes. Type I pneumococcus was found in the sputum, and the same organism was recovered from the blood-culture. Incidentally it may be stated here that Type I pneumococcus predominates in the reported cases of pneumococcus endocarditis.

The clinical *course* of the disease from the day of admission to the day of death may be noted in relation to the temperature range (in reproducing the temperature chart only the 5 A. M. and 5 P. M. temperatures are recorded). The patient seemed to improve during the first part of his stay in the hospital. The temperature, which had been dropping gradually after admission and to the tenth day, rose again, becoming intermittent during the last days of life. The signs in the chest showed very little change from day to day, except the friction sound disappeared shortly after admission. The redness, swelling, and tenderness over the dorsum of the right foot became localized, and the circumscribed area assumed the appearance of an abscess. An incision was made and a thick pus evacuated. Bacteriologic examination of the pus revealed Type I pneumococcus in pure culture, the same type of organism which had previously been recovered from the sputum and the blood. Without any evidences on examination of extension of the pneumonic process, the patient became rapidly weaker, chills occurred, and he died seventeen days after admission. The presence of a pneumococcus endocarditis was suspected, but nothing in the examination of the heart *per se* revealed anything other than that which is ordinarily found in pneumonia patients.

A *necropsy* was performed by Dr. Bauer of the Pathological Staff and revealed a resolving pneumonia of the left upper lobe, a vegetative aortic and pulmonary endocarditis, an abscess of the left rectus muscle, and a localized suppurating area involving the muscles and tendons on the dorsum of the right foot. The heart muscle was quite soft and flabby in appearance. The coronary vessels were not markedly tortuous or thickened. Examination of the valvular endocardium revealed large, smooth, yellowish-white papillary vegetations on

the free border of one of the aortic leaflets and on the pulmonary leaflets. Apart from the marginal vegetations the valves seemed normal and the orifices only slightly dilated. Swelling and congestion of the various viscera were noted, but no infarction.

Comment.—The interesting features of this case are: First, the isolation of Type I pneumococcus from sputum, blood-stream, metastatic abscess, and cardiac vegetations, and, second, the pneumococcus endocarditis involving the aortic and pulmonary leaflets. While pneumococcemia is common in pneumonia, the pneumococcus is recovered from the blood in only about one-third of the cases. Statistics vary greatly on this point, depending upon the technic and the stage of the disease in which blood-cultures are studied. The rarity of pneumococcus endocarditis in the presence of frequently occurring blood-stream infection is an interesting fact. Indeed, pericarditis is much more common than endocarditis. Acute endocarditis was recognized clinically in less than 0.5 per cent., while it was found at autopsy in almost 6 per cent. of the large series of cases of pneumonia collected by Norris and Farley. Locke in a recent analysis of 835 fatal cases of pneumonia found acute endocarditis in 30 cases, but in only 14 could the pneumococcus be recovered from the vegetations on the valve leaflets. Locke gives the incidence of pneumococcus endocarditis in pneumonia as 1.7 per cent.

Among all types of acute vegetative endocarditis Locke found in a series of 150 cases an incidence of approximately 9 per cent. due to the pneumococcus. Thayer reported in 1924, at the Meeting of the Association of American Physicians, a series of 206 cases of bacterial endocarditis, of which 28 were due to the pneumococcus, or approximately 13 per cent.

While acute pneumococcus endocarditis, like other forms of endocarditis, involves the left side of the heart more frequently than the right side, the relative frequency of right-sided involvement is greater. Thus Preble, who analyzed 141 cases of pneumococcus endocarditis, found that in 82.2 per cent. the valvular lesions were confined to the left side, in 12 per cent. to the right side, and in 5.7 per cent. were bilateral. Comparing this

with endocarditis in general, using Jürgensen's statistics, he found that the right heart is involved four times more frequently in pneumococcus endocarditis than in endocarditis in general. Other striking features which the comparison revealed are that the pneumococcus is something over twice as apt to involve the aortic valves as the other bacteria, and about one-third as apt to involve the mitral, while it attacks the tricuspid valve twenty times as often. In the light of Preble's and Jürgensen's tabulated experiences our patient would seem to be very unusual in the combination of aortic and pulmonary valve involvement without tricuspid or mitral involvement. The following table which is reproduced from Preble's article is interesting:

	Pneumococcus endocarditis cases (Preble).	Endocarditis in general (Jürgensen).
Aortic only	39.7 per cent.	18.7 per cent.
Mitral only	28.3 "	66.3 "
Aortic and mitral	14.1 "	9.2 "
Tricuspid only	8.5 "	0.4 "
Pulmonary only	3.5 "	2.3 "
Aortic, mitral, and tricuspid	3.5 "	1.0 "
Mitral and tricuspid	1.4 "	1.8 "

The symptoms of pneumococcus endocarditis do not differ materially from the other forms of acute bacterial endocarditis. The diagnosis from the physical signs referable to the heart may be difficult. The findings commonly found in the heart in pneumonia may cloud the developing endocarditis. Its presence should be suspected when the blood-culture is positive, and when evidences of metastatic infection are present, as in our patient. Symptoms suggesting infarction of various organs, such as pain and tenderness in the splenic area, pain over the kidneys with red cells in the urine, localized erythemata, or petechiæ in the skin and mucous membranes are of positive value in the diagnosis. Embolic phenomena are very common, since in approximately 80 per cent. of the cases the endocarditis is of the malignant type. The temperature of the pneumonia may drop to normal and be followed by an irregular, intermittent fever with the development of endocarditis; or the fever of pneumonia may

merge with that of the endocarditis. At times the patients complain of some vague discomfort, palpitation, or actual pain in the precordial region. The presence of an old cardiac lesion might be confusing if the cardiac history is not known. The presence of a pericarditis may add to the confusion. Arthritis and meningitis are frequently associated with the endocarditis.

Finally, it should be stated that pneumococcus endocarditis has been found without pneumonia, or at least with such atypical signs that the pneumonia was not discovered; and that while endocarditis in pneumonia is almost invariably pneumococcic, in a small percentage of cases other organisms, such as the streptococcus, may be the causative factor.

The course of pneumococcus endocarditis extends from a few days or weeks to several months, and ends almost invariably in death, although an occasional patient may recover.

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MULTIPLE MYELOMA. CLINICAL HISTORY. NECROPSY. PATHOLOGICAL STUDIES BY DR. J. R. PAUL. COMMENTS.

S. D., male, aged forty-two years, was admitted November 2, 1925 with a history that he had been treated vigorously for lues and had developed mercurialism. He had a chancre in 1905 and during the past year had complained of pains in the abdomen, back, and chest which had been assumed to be luetic in origin. The Wassermann reaction had been repeatedly positive. No evidence of mercurialism could be found after admission to the wards. Physical examination, however, revealed a man who was obviously quite sick. He was well developed, but poorly nourished. He seemed to have lost considerable weight. The temporal vessels were prominent, the eyes were prominent, the ocular movements normal, and the pupils reacted promptly to light and accommodation. The teeth were in poor condition. There was marked pulsation of the carotids. The thyroid was somewhat enlarged. The chest was emaciated, rounded, and symmetrical in outline, with prominence of the ribs and clavicles. The percussion note was hyperresonant throughout, the breath sounds were quiet. It was difficult to outline definitely the cardiac borders, although there was obviously no marked enlargement. The feeble apex-beat was palpable in the fifth interspace inside the midclavicular line. The aortic dulness was $10\frac{1}{2}$ cm. across in the first interspace. The heart sounds were clearly heard and the heart action was regular. A double murmur was audible over the aortic area. The liver margin was palpable about 5 cm. below the right costal margin in the right midclavicular line. The extremities showed no edema. The peripheral vessels were sclerotic and the pulse collapsing in type. The knee-jerks and ankle-jerks were sluggish. On several occasions on re-examination the patient complained of pain in the chest wall, especially on palpation and

percussion; at other times backache seemed to be the most annoying feature. He became progressively weaker and had the general appearance suggesting malignant disease. The entire body was searched for a malignant growth, but without result.

The laboratory studies revealed the following: Blood examination, hemoglobin 90 per cent., red blood-cells 4,320,000, white blood-cells 9650. The urine showed a heavy cloud of albumin with a few granular casts. The phthalein elimination was 65 per cent. in two hours. The Wassermann test was strongly positive.

The Roentgen-ray examination revealed nothing of note except an increased density of the hilus shadows, especially on the right side. An electrocardiographic study by Dr. Sweeney revealed a normal sinus rhythm with an auricular and ventricular rate of 60; no delay in conduction and moderate left ventricular preponderance.

While in the wards he became progressively weaker and more emaciated. The temperature was normal at all times and the pulse average from 60 to 90. The daily urine examinations during the first three weeks revealed an output varying from 1200 to 1800 c.c., a specific gravity from 1010 to 1026, a constantly present heavy cloud of albumin, and finely granular casts. After this period the microscopic appearance changed, casts were found only infrequently, although the heavy cloud of albumin continued. The phthalein elimination became reduced to 24 per cent. in two hours. The blood chemistry studies revealed: sugar 89 mg., creatinin 1.4 mg., and urea 48 mg. per 100 c.c. The blood examination one month after admission revealed hemoglobin 50 per cent., red blood-cells 3,900,000, and white blood-cells 10,000.

The problems of diagnosis in this case were not easy. It was obvious that an aortitis with dilatation which was probably luetic, moderate myocardial failure with enlargement of the liver, and chronic nephritis were present. However, the rapidly developing and progressive weakness with increasing pallor and emaciation seemed more rapid than ordinarily occurs in patients with these organic lesions. The clinical appearance resembled,

for example, that of a patient with carcinoma of the esophagus, although there was no evidence of this disease. As stated above, every possible search was made for a new growth, but this was not found. Just before death the respirations suddenly ceased, and the house officer, attempting artificial respiration, was startled by the sensation of cracking ribs when pressure was exerted on the thorax. It was obvious that an unusual brittleness of the ribs was present. That the diagnosis of multiple myeloma might have been made antemortem was evident when the roentgen-ray films of the chest were re-examined after death. These showed a wide-spread lesion of the ribs characterized by multiple small areas of bone absorption. At this point Dr. Paul, the Director of the Laboratories, will tell us of the necropsy findings.

DR. PAUL: The body showed advanced emaciation with evidences of cachexia. The skin was sallow, the eyes sunken, and there was marked atrophy of the muscles, particularly those of the extremities.

On opening the thoracic cavity one's attention was immediately focused on the unusual appearance of the ribs. Two ribs (the third and fourth) were found to be fractured in the region of the right midclavicular line. Many of them presented characteristic lesions which were easily demonstrable from within the chest cavities. These consisted of small, pea-sized, punctate fenestrations frequently associated with a moderate fusiform dilatation of the shaft. All of the ribs proved to be brittle. The bony tables were reduced in many instances to paper thinness; the marrow cavity was considerably enlarged and filled with soft, grayish, pulpy material. Similar lesions were noted in the sternum and, to a lesser extent, in the vertebræ. Actual deformity or gross enlargement due to tumor formation was not present.

Heart: A moderate degree of sclerosis of the coronary vessels was present, although the myocardium was not grossly scarred or hypertrophied. There was a noticeable deposition of fat in the papillary muscle of the left ventricle exhibiting characteristic tiger striping.

Aortic arch: Irregular thickening of the wall with wrinkling of the intimal surface began just distal to the aortic cusps. A large fusiform aneurysmal dilatation involved the ascending and transverse portions of the arch.

Lungs: Both presented the same picture. They were large, heavy, and showed an excess of fluid in the dependent portions.

Spleen, stomach and duodenum, and intestines: Essentially negative.

Pancreas: Due to the atrophy of the retroperitoneal fat this organ was unusually prominent. Scattered along both superior and inferior edges were many small yellowish-white, chalky, miliary areas.

Mesentery: The same chalky lesions were also seen in the retroperitoneal fat of mesentery and omentum.

Liver: This was relatively small and reddish-brown in color. A single white pea-sized nodule was noted on the surface, but on section about six or eight such lesions were encountered.

Kidneys: Both organs presented the same appearance. They were large and pale. The capsule stripped with relative ease, revealing a patchy smooth surface. The cortex was wide, measuring 16 cm. in thickness, and the structure appeared to be fairly regular. The pelves and ureters were negative.

Pelvis: No lesions similar to those noted in the ribs and vertebræ were detected in the pelvic bones. The pelvic organs were essentially negative.

Neck organs: Essentially negative except for the thyroid which was enlarged and presented a rather pale, beefy appearance. A large sharply circumscribed, calcified adenoma stood out as a chalky white mass in striking contrast to the rest of the organ.

The brain and skull were not examined.

Microscopic Examination.—Ribs: In sections taken from the areas which showed slight fusiform dilatation and fenestration of the shafts extensive erosion of the compact bone had taken place. The normal bone-marrow structure was obliterated and the marrow cavity filled with masses of loosely packed myeloma cells, morphologically of the plasma cell type. In general

structure these cells were slightly variable in size, being round, oval, or polygonal in shape with small round eccentrically placed nuclei, many of which actually protruded from the cytoplasm. As a rule these cells were mononuclear, although some of them showed two nuclei. No mitotic figures were observed.

Liver: The small pale nodules noted grossly proved to be discrete round collections of myeloma cells. They were sharply circumscribed and the adjacent surrounding liver cells showed only a moderate degree of atrophy.

Kidney: The picture proved to be of unusual interest. Marked thickening, edema, and diffuse round-cell infiltration was present throughout the interstitial tissue of the cortex and medulla. The tubules were universally dilated with flattening of the tubular epithelium, and within the lumen were many hyaline and cellular casts consisting of necrotic cells and polymorphonuclear leukocytes. The glomeruli were large, many appeared to be relatively undamaged, but, as a rule, adhesions between the tuft and capsule were demonstrable with associated scarring and hyalinization. The vessel walls showed moderate thickening without calcification. The most striking feature of the whole picture, however, was the extensive deposition of calcium throughout the cortex which appeared as irregular, bluish-staining amorphous masses ranging in size from that of a red cell to that of glomerulus. The location of these masses in the interstitial tissue was well limited to the cortex. As a rule the calcium masses seemed to be subepithelial in location, often actually compressing the tubule, and not infrequently they extended into and partially filled the lumen.

Pancreas: The miliary chalky areas noted grossly proved to be small islands of necrosis of fat and peripancreatic tissue which were extensively impregnated with calcium.

Thyroid: Diffuse impregnation with calcium of the adenoma, noted grossly, was present. The picture was not comparable to calcification of an area in which previous injury and cell damage had occurred, for the general structure and cells of the adenoma were well preserved, but the interstitial tissue and epithelial

cells alike all took up the hematoxylin stain to a rather marked degree.

Anatomic Diagnosis.—Multiple myeloma (plasma cell type) involving ribs, sternum, and vertebral column with metastatic nodules in the liver. Subacute nephritis with extensive cortical calcium deposition. Calcification of peripancreatic and retroperitoneal fat. Calcified adenoma of thyroid gland. Emaciation and secondary anemia. Fatty heart muscle. Syphilitic aortitis with fusiform aneurysm of the ascending and transverse aortic arch.

Comment.—From the pathologic aspect the case presents a number of interesting features. In view of the necropsy findings it does not seem surprising that the diagnosis was missed clinically, owing to the fact that, although the bone involvement was extensive, no palpable tumor masses were found. We did not, however, determine the exact distribution of the bone involvement in this case, as the skull and long bones were not examined. Scanty metastases to the visceral organs were present; they were detected only in the liver, and most of these were miliary in size.

In attempting to classify this case on the basis of the histogenesis of the myeloma cell it falls rather naturally into the group designated as plasmocytoma. As is well known, the origin of the cells of the multiple myeloma has been the subject of much discussion. It is assumed by many that these myeloma cells are derived from the undifferentiated bone-marrow cell, the ancestor of the leukocyte and the erythrocyte, but this assumption carries us into a discussion of the relationship between bone-marrow cells and plasma cells. There is no doubt that in this case the morphology of the great bulk of cells in the marrow cavity recalls vividly the picture of plasma cells. Not infrequently, however, groups of polygonal cells are found with dark pyknotic round nuclei which recall with equal vividness cells of the erythroblastic series.

One of the most interesting features of the case was the wide-spread deposition of calcium throughout the body, particularly in the kidney, thyroid, and retroperitoneal tissues.

In the kidney the picture is of extraordinary interest. A number of observations on the excessive excretion of calcium in cases of multiple myeloma have been made, notably those of Blatherwick, and Meyer and Cajori, and it seems probable that this phenomenon is directly associated with the rapid destruction of bone and abnormal liberation of large quantities of calcium in the body. The extensive calcium deposition in the visceral organs, particularly in the kidney in this case, is a striking picture which has, however, been described by a number of authors, notably by Tschistowitsch and Kolessnikoff, and perhaps the most interesting question which is forwarded by the findings in the case is that of relationship between the excessive calcium deposition in the kidney and the unusual renal lesion.

Concluding Comments by Dr. Funk.—Multiple myeloma was first described by Rusticky in 1873, and its rarity is attested by the fact that in 1920 Wallgren was able to find only 118 cases in the literature. It is considered a specific malignant tumor of the bone-marrow arising from a single cell type and characterized by multiple foci of origin in the skeletal system and only rarely metastasizing to other tissues. The frequent presence of Bence-Jones proteinuria and an inevitably fatal termination are characteristic of the condition. The ribs, sternum, and vertebra are chiefly involved; and less frequently the clavicles, cranium, pelvis, bones of the hands and feet, and the ends of the long bones. The effect of the growth is to thin the bones and make them brittle. Dr. Paul has referred to the pathologic features and the disturbances of calcium metabolism which occur.

The *onset* of the disease is usually *insidious* in middle and advanced age. Males are approximately twice as frequently affected as females. There is no known causative factor. The first symptom is usually *pain*, which early in the disease is periodic and later becomes constant. It is most varied in its location and the patient frequently refers it to "rheumatism" or "neuritis." To the physician various conditions more common than myelomatosis are suggested, for example, spondylitis, sciatica, pleurisy, intercostal neuritis, neuritis, etc. Pain in the

chest due to involvement of the ribs or sternum may simulate many intrathoracic diseases. In our patient the sternal discomfort was thought to be due to the aortic disease which was present. The multiplicity of the sites of pain is a striking feature in many patients. *Tenderness* over the painful bones may be present, but is not invariable. *Weakness* is an early symptom, and may, as in our patient, rapidly progress until a profound asthenia eventuates in death. The weakness is associated with loss of weight. Emaciation may become quite marked. Fever is usually absent. *Fractures* may occur following trivial injuries. Some years ago I saw a patient with multiple myeloma who fractured three ribs from violent coughing during an acute bronchitis. In one of the reported cases the pressure of a stethoscope caused a fracture of a rib. The unusual fragility of the ribs in our patient has been considered. *Deformity* due to small nodular swellings or larger protuberances, or a shortening of stature from curvature of the spine may be the first noticeable feature. A sternal tumor or a localized enlargement of the clavicle, or multiple nodular tumors connected with the bones may be distinctly visible. In one patient whom I saw there were at least a dozen small tumors connected with the bones in different parts of the body. Winkler observed 28 separate tumors in the skull. The presence of multiple tumors involving the skeletal system at once suggests the diagnosis. It is in the diffuse type of lesion that the diagnosis is overlooked. Only the most careful palpation of the bones will reveal the small surface irregularities in the diffuse type of lesion. In the patient reported in this clinic gross deformities of the bones were not obvious and the small nodulations of the rib found at necropsy were overlooked in the clinical examination.

The *blood-picture*, apart from the secondary anemia, shows no characteristic change. This is rather curious, in view of the marked involvement of the bone-marrow in the disease. Occasionally a few myelocytes are found in the peripheral blood. The presence of *Bence-Jones* proteinuria is generally considered as a frequent, although not a specific characteristic of the disease. Unfortunately in our patient no test was performed for

this substance. Its absence, however, does not negative the diagnosis. Hansen found it present in only 1 of the 7 cases which he studied. Bradshaw, on the other hand, observed a patient in whom Bence-Jones proteinuria was discovered one year before the appearance of the bone tumors, and his attention to the diagnosis was directed by the urinary finding.

Perhaps the most valuable aid in diagnosis is rendered by the *Roentgen-ray examination.* In the absence of gross bone tumors the findings of the films may be overlooked, as in our case, unless carefully searched for. In a case recently reported by Wood and Lucké films taken four months previously and passed upon as normal by a number of surgeons and roentgenologists were considered as showing evidence of myeloma by Pancoast. The examination of the bony parts of the chest, as well as the soft tissues, should be the rule in every Roentgen-ray study. The characteristic feature of the bone changes is the presence of multiple areas of diminished density which correspond to areas of calcium absorption and replacement by soft tumor tissue. The surface regularity of the bones is lost. Gross nodular protuberances may be present. A characteristic roentgenographic description is that which Meyer and Cajori give in relation to the sternum in their patient: "Innumerable distinct tumors were present, making the photograph of the sternum look as though it contained innumerable bubbles."

The *course* of the disease varies from a few months to a few years and is inevitably fatal. There is no known treatment at present which has the least influence on the disease.

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CLINIC OF DR. G. HARLAN WELLS

HAHNEMANN HOSPITAL

REPORT OF A CASE OF CHRONIC PHOSPHORUS POISONING (PHOSSY JAW)

To the physician of today chronic phosphorus poisoning, that most disfiguring and loathsome of all of the industrial diseases, is, fortunately, a clinical curiosity. Dr. Alice Hamilton, Professor of Industrial Medicine at Harvard University, informs me that no known case of this character has occurred in the United States since Congress enacted a law abolishing the use of white phosphorus in the match industry in 1912. The disease has also been banished from Europe as the result of the International Congress at Berne, Switzerland, in 1908, at which time all of the countries of Europe agreed to forbid the use of white phosphorus in the manufacture of matches.

Owing to the fact that the Constitution of the United States does not permit the national government to interfere with the industries of our various States, Congress was compelled to accomplish its purpose by imposing a prohibitory tax upon matches made from white phosphorus, but this law does not apply to other articles made from poisonous forms of phosphorus.

The case that I shall present to you today developed in a patient employed in the manufacture of fireworks, from a paste containing white phosphorus.

The history of the patient is as follows:

Catharine F—— at the age of sixteen entered a fireworks factory in the latter part of November, 1921. At that time she was a well-developed country girl in excellent health, with perfectly normal teeth. Her duties consisted in wrapping in tissue paper small amounts of a paste containing white phosphorus. This paste was about the consistency of flour paste and was made in an adjoining room in the following manner:

Gum arabic was heated in hot water and white phosphorus in stick form was added. After the phosphorus was melted the mixture was thoroughly

Fig. 8.—Shows swelling of cheek and lower lip and the peculiar protrusion of the eyes. April, 1924.

Fig. 9.—Shows discharging sinuses below in the left inferior maxillary region. April, 1924.

stirred until cool. Carbonate of magnesium and red clay were now added, and finally chlorate of potassium. The paste contained about 4 per cent. of

white phosphorus. Phosphorus fumes arose almost continuously from the paste after the magnesium carbonate was added until the wafers into which the composition was molded were thoroughly dry.

After the mixture was completed it was carried in a big tub into the room where Catharine and other employees worked. Each of the employees filled their pans with the composition and placed it beside them on the table at which they worked. Each employee had a spoon and a mold. They placed a bit of tissue paper in the mold, took a little of the paste on a spoon,

Fig. 10.—Shows discharging sinus in the right inferior maxillary region. April, 1924.

poured it on the tissue paper, then with their fingers twisted the paper around and molded the wafer.

Inadequate provisions were made for ventilating the workroom and phosphorescent fumes were in the air in appreciable amount. The paste, which was of a sticky character, adhered quite freely to the fingers of the employees, also to their clothing, and at times even to their faces.

Catharine first started to work with the phosphorus paste in November, 1921, and continued this work about six months. After a vacation of three weeks, she resumed her duties in September, 1922, and continued with this work until June, 1923, with brief intermissions.

Fig 11.—Showing condition of the right inferior maxillary region in April, 1926.

Fig. 12.—Showing left inferior maxillary region April, 1926. Sinuses on both sides are still discharging pus three years after onset of the necrosis of the jaw.

The first disturbance in health observed by Catharine was an irritating cough, unaccompanied by any expectoration, in January, 1923. Soon after this she began to feel unusually tired, her appetite became impaired, and two teeth in the lower jaw showed signs of caries. In March, 1923 these two teeth were extracted, but the wound did not heal. In April, 1923 she developed considerable fever and was confined to bed for two weeks. During this time the wound in the lower jaw was discharging pus and necrosis of the bone was taking place.

She returned to work in the factory about May 1st and continued to handle the phosphorus paste until June, 1923. During the summer of 1923

Fig. 13.—Right inferior maxilla. December, 1923. Note extensive area of necrosis.

the condition of her jaw became progressively worse, and in September, 1923 she came to Philadelphia and was examined by Dr. N. F. Hoffman at the Children's Homeopathic Hospital, and a diagnosis of phossy jaw was made. At that time there was bilateral necrosis of the lower jaw and several of the lower teeth had become loosened. Numerous operations were performed at various times for the removal of loose teeth and of necrosed bone, but the condition still continues, although a period of three years has now elapsed since the first signs of necrosis of the jaw developed.

The patient first came under my personal observation in November, 1923. At that time the local necrosis was very active and there were large sinuses discharging pus from both sides of the neck below the jaw. The pa-

tient had lost considerably in weight, could swallow food only with great difficulty, and exhibited a septic type of fever which ranged from 99° to 104° F. daily. A careful examination of the lungs revealed no signs of tuberculosis or other pulmonary pathology. The *x*-ray examination of the lungs was negative. The sputum contained no tubercle bacilli, nor did the discharge from the wounds or the scrapings from the bone.

The heart was normal in size and position; no valvular lesion was detected; the muscle tone of the heart was decidedly weakened. The pulse was rapid and feeble, but regular.

Fig. 14.—Left inferior maxilla. December, 1923. Note extensive area of necrosis.

The blood examination showed evidence of a decided anemia with an increase in the leukocyte count. The Wassermann test was repeatedly negative.

The urine analysis showed no abnormality.

Radiographs of the jaw showed extensive bilateral necrosis involving the rami of both mandibles and extending backward to the angle of the jaw. The entire anterior portion of the jaw seemed to be separated from the rami. Radiographic films were made of the various long bones of the body, but no pathologic changes could be demonstrated.

The plan of treatment adopted by Dr. Herbert Leopold, the surgeon in charge, was to secure good surgical drainage, to remove loose portions of bone from time to time, and to build up the general health of the patient by a nutritious diet and by keeping her in the fresh air as much as possible.

After six months of treatment along these lines the septic fever began to drop and gradually the temperature reached

Fig. 15.—Right inferior maxilla. April, 1924.

normal. As the septic condition improved the pulse became less rapid, fuller in volume, and the tone of the heart muscle improved. During the past two years the patient has gradually improved in general health. She has gained several pounds in weight, has a good appetite, and seems to be in a satisfactory condition as far as her general health is concerned.

The necrosis of the bone, however, still continues, and, while the amount of discharge has lessened, there are still sinuses on

both sides of the neck from which pus is constantly exuding. All of the lower teeth have fallen out except the four incisors, which are loose. On inspecting the mouth we observe a large piece of bone in the left lower side of the mouth which shows distinct necrotic changes. It would seem probable that at least two or three more years will elapse before all of the necrotic

Fig. 16.—Left inferior maxilla. April, 1924.

bone will have been cast off and the jaw replaced by the formation of new bone.

The modus operandi in these cases is as follows:

The fumes of the phosphorus, and perhaps small particles of the element itself, come in contact with the saliva in the mouth and result in the formation of phosphorous and phosphoric acids. These acids attack the enamel of the teeth, and, especially if a carious area is present, they set up a rapid process of necrosis which involves not only the teeth but also the bony

structures of the jaw as well. The process that takes place in the bone is an ossifying periostitis, the formation of new bone taking place under the periosteum as the older bone is destroyed.

Some writers hold the view that the action of phosphorus in those cases of long-continued exposure is constitutional, and that a local necrosis of the bones of the jaw is the result of a specific affinity of the phosphorus acting through the blood-stream.

Fig. 17.—Right inferior maxilla. August, 1925.

This view would appear to be disproved by the fact that animals fed on phosphorus develop symptoms of constitutional poisoning without any evidence of necrosis of the jaw. There is no doubt, however, that phosphorus does have a decidedly injurious effect upon the general health of the patient, and the impairment of resistance may be a factor in the development of phossy jaw.

The constitutional symptoms of phosphorus poisoning—viz., loss of appetite, emaciation, anemia, and bronchitis—all occurred in the patient now before us. It must be borne in mind, however,

that many if not all of these symptoms may have been the result of the prolonged and severe sepsis that has existed.

A few cases of chronic phosphorus poisoning have been reported in which brittleness of the long bones developed, and Ringer states that extensive changes occur in the epiphyses of the long bones. In the present patient a careful examination of the long bones, supplemented by *x*-ray studies, failed to reveal any pathologic changes.

Fig. 18.—Left inferior maxilla. August, 1925.

I have presented this patient to you for two reasons:

First, that you may have the opportunity of seeing a rare disease that I trust none of you will ever see again.

Second, that having witnessed the deforming and incapacitating results of chronic phosphorus poisoning, you will be stirred to lend your aid in the efforts that are being made to prevent the use of white phosphorus in American industry.

The history of the use of phosphorus in the match industry shows conclusively that phossy jaw arises entirely from the use of white phosphorus. The red or morphous phosphorus is practically harmless, and sesquisulphid of phosphorus, from which the modern match is made, can be used with entire safety in industry.

In the manufacture of many fireworks white phosphorus is still extensively used under conditions which in numerous instances are far from sanitary. The occurrence of other cases like the one just presented is, therefore, exceedingly probable.

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A CASE OF PYOPNEUMOTHORAX ILLUSTRATING THE DIFFERENTIAL DIAGNOSIS OF ACUTE INFLAMMATORY DISEASES OF THE CHEST AND ABDOMEN

VERY frequently we hear physicians severely criticised for their failure to recognize acute inflammation of the appendix or of the gall-bladder at an early stage of the disease, with the result that operation is delayed until gangrene has set in.

We have all, probably, been guilty of such an error, and fully recognize its serious results. On the other hand, it has been my fortune, or misfortune, to see many cases subjected to abdominal section for the purpose of removing the appendix or gall-bladder when these organs were found to be entirely normal, and the real trouble after the operation was discovered to be in the chest.

About two years ago I was called to see a patient who had developed an acute attack of abdominal pain in the right side associated with marked rise in temperature. His abdomen was opened and the appendix removed, but the fever persisted. The case was then diagnosed typhoid fever, and was treated as such for a period of six weeks. At the end of that time the fever still persisted, and I had the opportunity of aspirating the patient's chest and demonstrating the presence of an empyema which had been present for several weeks.

This confusion of acute inflammatory diseases of the chest and of the abdomen is so common that we must ever be on the alert. "Short-cut rules," such as "pain in the right lower abdomen means appendicitis," sound very well; the only disadvantage of such a rule is that it is not true.

The case that I will now present is a striking example of the difficulties that confront us in the differential diagnosis of this group of cases.

The history of the patient is as follows:

Charles C., twenty years of age, a clerk by occupation.

Family History.—Father and mother are living and well. There are no other facts of importance in the family history.

Past Personal History.—The patient had scarlet fever at five years of age. He was then in good health until October, 1925, when he contracted lead colic while working in a storage battery plant. He does not use alcohol, coffee, or any drugs.

History of the Present Illness.—On December 20, 1925 the patient developed acute coryza, which was followed by bronchitis. He had a slight cough

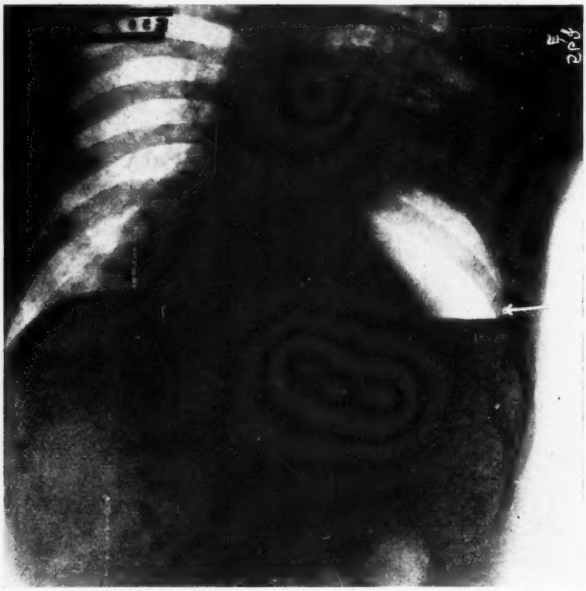

Fig. 19.—Patient in standing position. Note the horizontal level of the fluid in the right side of the chest with the air space above it extending upward about 3 inches.

with the expectoration of a small amount of mucus, but no fever. He was apparently convalescing from this condition, and on January 11, 1926 he was suddenly seized, while at work, with pain in the right lower quadrant of the abdomen. This pain was located at McBurney's point and was drawing in character. The patient was nauseated, but did not vomit. He was immediately put to bed and an ice-bag applied to the lower right quadrant of the abdomen. The following day he was brought to the Hahnemann Hospital because the pain had increased in severity and the patient had had one

or more chills. His temperature ranged from 100° to 104° F.; his pulse, from 90 to 110; and the respirations, from 26 to 28 per minute.

The physical examination of the abdomen revealed marked tenderness and rigidity over the entire right side of the abdomen. The maximum tenderness on pressure started from McBurney's point and extended upward for about 2 inches. There was also distinct tenderness over the region of the gall-bladder. Examination of the chest showed the respiratory movements to be shallow and thoracic in character. On percussion no area of abnormal

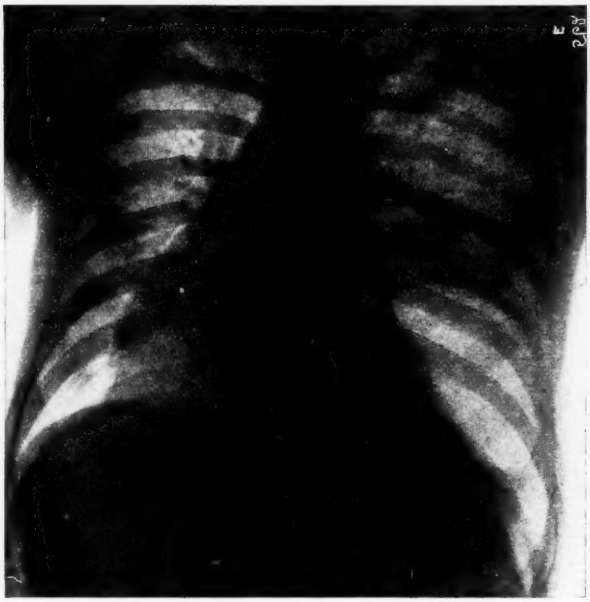

Fig. 20.—Patient in the recumbent position. The cavity containing air is distinctly visible, but the horizontal line of fluid has disappeared.

dulness could be detected. On auscultation no râles or friction-rub could be heard, the respiratory murmur appeared to be normal, the transmission of the spoken and whispered voice was normal. The leukocyte count was 16,300. The differential count was as follows: Polynuclear leukocytes, 91 per cent.; lymphocytes, 8 per cent.; transitionals, 1 per cent.

A provisional diagnosis of acute appendicitis was made.

The examination of the consulting surgeon revealed the following:

Rigidity of the right rectus muscle with tenderness extending from the outer edge of the right rectus outward over the lateral gutter. Posteriorly,

over the kidney area, there is exquisite tenderness with marked rigidity of the lumbar muscles. Provisional diagnosis: Acute pyelitis.

The patient was put in the Fowler position and saline solution was administered continuously by rectum. An analysis of the urine was made, which showed the following: Specific gravity 1.021, reaction acid, albumin a trace, sugar 1.2 per cent., acetone absent, microscopic examination showed a few hyaline casts, a few pus-cells, and some epithelium.

The following day the pain was slightly diminished and there was some remission of temperature and in the pulse rate. The tenderness over the kidney area continued to be quite acute, while the tenderness over McBurney's point was slightly less than it had been previously.

During the next two days the abdominal pain and rigidity gradually ameliorated, although there was still slight tenderness on pressure over the kidney. On the fourth day after admission to the hospital dulness was observed over the lower portion of the right chest posteriorly. No friction-rub was detected; focal fremitus was diminished and the breath sounds were faint. These sounds suggested a thickening of the pleura or a possible pleural effusion. The following day a puncture was made in the right side of the chest in the eighth interspace in the midscapular line and 40 c.c. of a bloody, purulent fluid was withdrawn. Examination of this fluid showed the presence of a large number of pus-cells and red blood-corpuscles. The fluid was cultured and the pneumococcus was found to be present.

Three days later a physical examination revealed an area of hyperresonance in the right side of the chest in the posterior axillary line, extending from the eighth up to the sixth rib. Below this area there was pronounced flatness. A radiographic examination showed the presence of encysted fluid in the lower portion of the right chest, and above the fluid a partially collapsed lung. The level of the fluid was horizontal with the patient in the standing position. These signs, together with radiographic findings, showed that we were dealing with a pyopneumothorax.

As the amount of fluid in the right chest was obviously small, it was decided to wait a few days before resecting a rib and providing surgical drainage. The chest was aspirated again and a few cubic centimeters of purulent fluid withdrawn. Preparations were made for the injection of acraflavin into the cavity, but on puncture two or three days later no fluid could be withdrawn. The temperature also showed signs of remitting, and it was therefore decided to continue expectant treatment. Temperature dropped by lysis, and the patient made a gradual recovery. A radiographic examination of the chest two weeks later showed the fluid was completely absorbed and the lung had expanded and entirely filled the cavity.

This case illustrates two important facts: First, that the physical signs of an acute pleural inflammation may be very obscure in the early stage of the disease, and second, that the differential diagnosis between acute inflammatory conditions in the chest and in the abdomen is at times very difficult.

Owing to the fact that acute surgical diseases of the abdomen frequently demand immediate operative procedures if the life of the patient is to be saved, it is often a matter of supreme importance to be able to exclude non-surgical diseases of the abdomen and acute inflammatory processes in the chest. In this case the pain was in the right side of the abdomen, and in such conditions it is necessary to differentiate the following diseases:

1. Acute appendicitis.
2. Acute pyelitis.
3. Renal colic.
4. Pyonephrosis.
5. Acute cholecystitis.
6. Acute pancreatitis.
7. Acute gastro-intestinal disturbances.
8. Acute salpingo-oöphoritis.
9. Typhoid fever.
10. Gastric ulcer.
11. Duodenal ulcer.
12. Bowel obstruction.
13. Neuritis of the ileo-inguinal nerve.
14. Acute pleural or pulmonary inflammation.

The classical symptoms of *acute appendicitis*—viz., pain, nausea, localized tenderness, and muscular rigidity—are so well known that it seems superfluous to repeat them. Unfortunately, however, appendicitis presents itself under such various forms and manifestations that every case requires careful scrutiny, and no short-cut rules of diagnosis can be followed with safety. The pain in acute appendicitis is usually severe, is often sudden in onset, and is of a colicky nature. Nausea and vomiting are frequently absent and cannot be relied upon as diagnostic symptoms. Localized tenderness in the right iliac fossa is an almost constant symptom. This tenderness is quite superficial and is frequently associated with a cutaneous hyperesthesia. Frequently an examination through the rectum or the vagina will reveal marked tenderness in the right iliac fossa, especially if the appendix points downward. When the appendix points upward the tenderness may be in the region of the kidney,

and may even be confused with the tenderness of an inflamed gall-bladder.

Muscular rigidity is a very valuable symptom and one which is rarely absent.

The pulse is usually accelerated, and a gradual increase in the pulse rate is ordinarily a sure sign of a progressive inflammation. The temperature usually rises very early in an attack. In the milder cases it may be no higher than 100° or 101° F., but in the more severe cases the temperature reaches 102° or 103° F. A sudden drop in temperature, if accompanied by a rise in the pulse rate and an increase in rigidity, is indicative of gangrene or of beginning peritonitis.

Appendicitis is almost invariably accompanied by leukocytosis, in milder cases the count ranging from 10,000 to 12,000. A steadily increasing leukocyte count, especially if it exceeds 15,000, is indicative of a severe infection. A sudden drop in the leukocyte count may be indicative of gangrene or of a perforation.

The presence of an inflammatory swelling in the right iliac fossa can rarely be made out in the early stage of the disease. A distinctly palpable tumor usually indicates that the omentum has wrapped itself around the appendix, or a localized peritonitis has taken place, with probably abscess formation.

Acute pyelitis is frequently accompanied by considerable abdominal pain with marked tenderness, and at times rigidity, which is characteristically found 2 or 3 inches above McBurney's point. There is often distinct tenderness posteriorly in the lumbar region. The diagnosis is confirmed by *the presence of pus in the urine.* Red blood-corpuscles are frequently present. The amount of albumin is moderate unless an acute nephritis coexists. If one or more specimens of urine can be obtained, it is usually easy to confirm or disprove the existence of a pyelitis. In rare instance catheterization of the ureter may be necessary to confirm the diagnosis.

Renal colic is usually readily differentiated from appendicitis. The pain is intense and frequently associated with symptoms of collapse, such as a rapid, feeble pulse, and coldness of

the skin and extremities. Occasionally the pain begins in the lumbar region and radiates along the course of the ureter to the testicles and thigh. Frequency of urination is common and the urine usually contains either macroscopic or microscopic blood. Fever, as a rule, is absent and there is no leukocytosis. The *x*-ray will frequently settle the diagnosis if any doubt exists.

Pyonephrosis.—This condition is usually of a chronic type. The enlarged kidney can often be felt, there is no rigidity of the abdominal muscles, and no fever. In most instances there is a history of abdominal pain which has existed for some time.

The pain in *acute cholecystitis*, whether accompanied by gall-stones or not, is usually in the right upper quadrant of the abdomen. Where the liver is markedly displaced downward, however, the pain may be at the level of or even below the umbilicus. The pain is sharp in character and frequently radiates to the scapular region. The right rectus muscle is distinctly rigid. In some cases there may be a palpable tumor in the region of the gall-bladder or there may be a history of jaundice. A leukocytosis is usually present. The fever may be persistently high or may be decidedly irregular if empyema of the gall-bladder develops.

Acute Pancreatitis.—This condition is ushered in with a sudden severe pain in the epigastric region accompanied by vomiting and symptoms of collapse. There is distinct tenderness and muscular rigidity in the epigastric region. The pulse is rapid and often feeble. The temperature is often subnormal and rarely above normal, unless suppuration occurs.

Acute Gastro-intestinal Disturbances.—In this group of conditions the pain is ordinarily not as severe as in appendicitis, and is usually felt in the epigastric region or above the umbilicus. There is no localized tenderness or rigidity, and the symptoms often subside when the bowels have been thoroughly evacuated. Fever and a leukocytosis are absent.

Acute Salpingo-oöphoritis.—The differential diagnosis in acute inflammations of the tube and ovary is usually made by a vaginal examination which reveals a tender mass alongside of or behind the uterus. The pain is usually low in the abdomen.

There is but little rigidity. Tenderness on palpation is considerably below McBurney's point. Nausea and vomiting are infrequent. There is frequently a history of infection of the uterine or vaginal tract.

Despite the fact that *typhoid fever* and appendicitis differ widely in many of their clinical and laboratory aspects, the two diseases are frequently confused. The following points will usually enable us to make a differential diagnosis: To begin with, the pain and rigidity are much less pronounced in typhoid fever than in appendicitis. In typhoid fever there is a leukopenia. In the early stages of typhoid we can usually get a positive blood-culture, and in the late stages, a positive Widal reaction. The spleen is enlarged and the rise in temperature is more gradual, with a relatively low pulse rate. If there is any doubt at all, the laboratory examination of the blood, of the stools, and of the urine will settle the diagnosis.

Gastric ulcer is generally preceded by a history of chronic indigestion and by attacks of pain in the epigastric region which show a singular regularity in their relation to food, and which are usually relieved by vomiting or the use of alkalies.

Duodenal ulcer also is associated with a history of pain of long duration felt in the upper abdomen, and usually coming on three or four hours after a meal.

Perforated ulcer of the stomach or of the duodenum may be very difficult to differentiate from appendicitis. The pain in this condition is higher up in the abdomen than that of appendicitis. The point of greatest tenderness is either in the epigastric region or in the right iliac fossa on a level with the umbilicus. There is frequently a previous history of tarry stools or a hematemasis. The muscular rigidity is very pronounced, and the abdomen is often retracted until the tympany due to peritonitis results from gradual distention.

Bowel Obstruction.—The differential diagnosis in the first forty-eight hours is readily made. Nausea and vomiting are persistent symptoms. The bowels cannot be evacuated nor can flatus be passed. Abdominal distention appears early and is

pronounced. The temperature and pulse before the onset of peritonitis are normal. There is little or no change in the leukocyte count.

Neuritis of the Ileo-inguinal Nerve.—I have seen more than one case of this type diagnosed as acute appendicitis. The pain is severe, there is often decided cutaneous hyperesthesia, but frequently, on deep pressure, little pain is experienced. There is no true muscular rigidity, the temperature is normal, and there is no increase in the leukocyte count. Nausea and vomiting are absent.

Both *pneumonia* and *pleurisy* are capable of setting up severe abdominal pain, especially in children. In the pneumonic cases, even though the physical signs may be obscure, the differentiation can frequently be made by the history of a chill, the presence of a cough, high respiratory rate, and a high pulse rate. The leukocyte count in pneumonia is likely to be higher than in appendicitis, and a blood-culture may be positive for the pneumococcus. The abdominal pain is seldom distinctly localized over one organ, and the muscular rigidity is not as circumscribed or as constant a feature.

In some respects pleurisy is more difficult to differentiate than pneumonia because the respiratory rate, the pulse rate, and the leukocyte count in pleurisy are frequently similar to appendicitis. Once a friction-rub can be detected, the differential diagnosis can be readily made, but in the diaphragmatic form of pleurisy and in the parietal types in which a friction-rub cannot be detected, great confusion may exist. In most cases of pleurisy the patient's breathing is shallow and the pain is usually definitely aggravated by taking a deep breath or by coughing. The presence of a distinct cough would favor a diagnosis of pleurisy rather than appendicitis. Vomiting is often absent in pleurisy. The abdominal pain is usually diffused over the entire right side of the abdomen and often extends upward to the chest. The muscular rigidity does not always bear a distinct relationship to the severity of the pain or to its amelioration and aggravation. A rectal or vaginal examination may be of considerable help in arriving at a proper conclusion.

In some cases a policy of "watchful waiting" may have to be adopted, with frequent observations of the patient, supplemented by careful and repeated laboratory studies of the blood and urine. Such a course may prove less harmful to the patient than hurried operations based upon inaccurate diagnosis. All doubtful cases, however, should be removed to a hospital for observation, where surgical procedures can be instituted without delay should definite indications for operation develop.

THE CHEVALIER JACKSON BRONCHOSCOPIC CLINIC, UNIVERSITY HOSPITAL

CLINIC OF DR. GABRIEL TUCKER

CASE I. PEANUT IN THE LEFT LOWER LOBE BRONCHUS

Dr. O. H. Perry Pepper.—This patient was referred to me by Dr. Ravdin, of the Surgical Service, who asked me to go over him from the medical standpoint. Patient is a boy ten years old, who last June, while eating peanuts, choked. His mother has recognized a wheeziness as being present from then on, although the wheeze did not figure as largely in the minds of the medical man as in the mother's mind. By August he was quite sick and was taken to the hospital with a diagnosis of bronchial pneumonia. This diagnosis is not an uncommon one in these cases of foreign body. *x*-Ray showed a suspicion of a pleural effusion, and the introduction of a needle was advised. The following day the *x*-ray showed considerable pneumothorax, which complicated the case, and which we believe was incident to the insertion of the needle for the pleural effusion which was not present.

When I saw the patient he was running a little fever and increase of signs in the lung. He had when I saw him the same wheeze that the mother had commented on, and this could be heard by placing the ear near the mouth. The right lung seemed to be very centrally placed, but appeared to be negative. On approaching the left lung with the stethoscope one was struck by the fact that there was moisture over the left lower lobe, and that on listening to the left lower bronchus one could hear again the wheeze which the mother had reported. Expiration was long and wheezing, such as you would expect to hear if the

bronchus was partly occluded. It seemed very clear cut. Two or three days later I saw him again, and his physical signs were very much more marked, and at this time it would have been much less difficult to make a diagnosis. The moisture had temporarily disappeared. I had a feeling that the correctness of localization was aided by his having an actual flare-up of signs with moisture centering in the left lower lobe. From these signs we made a diagnosis that a peanut had been inhaled into the left lower bronchus. This differed from the *x*-ray diagnosis, which stated that the *x*-ray showed no evidence of anything in the left lower lobe. The amount of moisture present would have led one to expect increased shadow. Dr. Tucker operated on the patient yesterday, and removed the peanut bronchoscopically, and I need only say that the mother tells me this morning that during last night she arose four times and went to see if the child was alive because he was sleeping and breathing so quietly, for the first time since last June. This morning the wheeze is entirely gone. There are many râles in both lungs today, probably as the result of the escape of the fluid which has been held back in the lungs due to the foreign body.

This case has been a very instructive one for me.

Dr. Gabriel Tucker.—As Dr. Pepper has stated, we removed bronchoscopically a portion of peanut kernel from the left lower bronchus (Fig. 21). The child was given morphin sulphate (grain $\frac{1}{8}$), atropin sulphate (grain $\frac{1}{300}$) hypodermically one hour before bronchoscopy, and no general or local anesthesia was used at the time of the operation. We found in this case that the peanut was in the lower lobe bronchus distal to a ring of swollen edematous mucosa in the main stem of the lower lobe, and caused the type of obstruction known as "ball valve." In this case, as Dr. Pepper stated, Roentgen-ray examination was not positive for foreign body in the left lung. The roentgenologist does not look for the shadow of the foreign body, but for evidence of obstructive emphysema and obstructive atelectasis distal to the foreign body. The presence of obstructive emphysema and obstructive atelectasis is determined both by fluoroscopic and

film examinations, and gives a very definite means of localization of the foreign body when present. Dr. Jackson has described the mechanism which we demonstrate bronchoscopically that produces the phenomenon of obstructive emphysema and obstructive atelectasis under three types of valve obstruction, namely, the by-pass valve or ball-valve, the check-valve, and the stop-valve. In the by-pass type of obstruction air passes the foreign body on both inspiration and expiration. The *x*-ray examination in this type of case is very likely not to give positive information. In the second type of obstruction, the check-valve, the air passes on inspiration into the lung, due to the fact

Fig. 21.—Case I. Portion of peanut kernel removed from the left lower lobe bronchus of boy ten years old. He had choked while eating peanuts and immediately developed a wheeze which persisted until bronchoscopic removal of peanut, six months later.

that there is inspiratory widening of the bronchial lumen at the point of lodgment of the foreign body. On expiration the bronchial lumen narrows and the air does not pass out, but is trapped in that portion of the lung distal to the foreign body. In this type of case we have obstructive emphysema. The third type, the stop-valve, occurs where the foreign body completely blocks the bronchus due to the shape of the foreign body filling the bronchial lumen completely in some cases. In other cases the foreign body swells and causes complete blocking, and in other cases the inflammatory reaction around the foreign body is such that no air passes on either expiration or inspiration. In this type of case the absorbtion of the air in the lung distal to the

point of lodgment of the foreign body produces obstructive atelectasis. We have had in the clinic over 200 cases of vegetal foreign body, so that we may state that the cases are not unusual.

CASE II. KEWPIE DOLL IN THE LARYNX

THIS child, four years of age, was admitted to the University Hospital ten days ago at 3 o'clock in the morning. She had been brought up from the Eastern Shore of Maryland by automobile, and on admission she was urgently dyspneic, with marked retraction at the suprasternal notch and at the tip of the ensiform cartilage. She showed the typical signs of laryngeal dyspnea. Emergency tracheotomy was done on admission.

The history was that at 5 o'clock the same evening she had choked on a small celluloid kewpie doll. Following the accident the dyspnea had become progressively worse up to the time of her admission, when respiratory efforts had almost ceased. A low tracheotomy was done, and breathing restored by artificial respiration. The dyspnea was entirely relieved by the tracheotomy. The child was put to bed to react from the shock, and the following day, after her general condition had returned to normal, a direct laryngoscopy without anesthesia showed a foreign body in the subglottic area of the trachea. This was removed through the mouth and was found to be a celluloid kewpie doll (Fig. 22). There was very little swelling of the larynx and trachea, and air passed freely through the larynx. The tracheotomy tube was left in position until the wound closed around the tube. A complete cork was worn for three days and three nights, the child breathing without difficulty through the larynx. The tube was removed yesterday, and the child is now ready to go home.

I would like to say a word about the technic for tracheotomy. Low tracheotomy is always done. The front of the neck is split open vertically from the thyroid to the suprasternal notch, and the wound is left open, bleeding points are ligated, and the skin is not closed with sutures, but is dressed with a large square of gauze moistened with 1 : 10,000 bichlorid, and is changed every two hours without removing the tube. By this technic no scar results. There is practically no infection in the neck, and if

the tube is inserted below the second tracheal ring (the third, fourth, and fifth rings being cut) there will be no stenosis caused by the tracheotomy tube, and it can be removed as soon as the laryngeal stenosis has been cured.

Fig. 22.—Case II. Kewpie doll removed through the mouth from the larynx and trachea of a child four years of age, following a choking attack. The child became progressively more dyspneic, respiratory effort having almost ceased on her admission to the University Hospital. Low tracheotomy relieved the dyspnea before any attempt was made to remove the foreign body.

The tracheotomy was done for the relief of the laryngeal dyspnea and not for the removal of the foreign body or the insertion of the bronchoscope. The bronchoscope can be inserted more easily and with greater safety through the mouth, if the proper bronchoscopic technic is followed, than through the tracheotomy wound.

BRONCHOSCOPY IN DISEASE

CASE III. BRONCHIAL ASTHMA

WE have already considered bronchoscopy in non-tuberculous suppurative pulmonary diseases in Dr. Muller's symposium on lung abscess. We should like to show you, however, this man, thirty-two years of age, referred to the clinic by Dr. Richard A. Kern, from the Asthma Clinic. He had the typical asthmatic attacks, and Dr. Kern had made the routine studies as to allergy and found them negative. He was referred for diagnostic bronchoscopy and the taking of an uncontaminated swab specimen of the bronchial secretions for culture and autogenous vaccines. On bronchoscopic examination he showed the typical findings of asthma: the mucosa of the trachea and larynx were thickened, and there was thick, tenacious, mucopurulent secretion in the trachea and main bronchi, with evidence of the usual expiratory difficulty. The man's condition improved markedly following the bronchoscopy. The autogenous vaccine was prepared and administered, and he was discharged at the end of a month entirely relieved of his asthma. He went to his home in central Pennsylvania, and after a period of six weeks his asthmatic attacks returned, and he came back to the Asthma Clinic and told them that he wished to have further bronchoscopic treatment, and that he felt that his improvement dated from the time of his bronchoscopy. Dr. Kern referred the patient back to the clinic, and we treat him today for the fourth time. He is very much better, the appearance of the tracheobronchial mucosa shows marked improvement; the secretions are much less in quantity, show no pus, and the patient is able to get rid of the secretion with very little difficulty. In cases where asthmatic symptoms are associated with tracheobronchitis, bronchoscopic aspiration and local medication is of very decided benefit in the treatment of the patient. That the man felt relieved is evidenced by the

fact that he returned of his own accord for further bronchoscopic treatment.

CASE IV. PAPILLOMATA OF THE LARYNX

The first case I wish to show you of papillomata of the larynx is in a child five years of age. He was referred to the Clinic by Dr. Justin M. Waugh, of Cleveland, Ohio, on account of dyspnea and aphonia, with a diagnosis of multiple recurrent papillomata of the larynx. Following an attack of whooping-cough which began when the child was six months old, and lasted six months, he became aphonic, and gradually dyspneic, the dyspnea becoming very marked on exertion. He was treated by a number of physicians, and, finally, when three years of age, Dr. Waugh was consulted, and referred him to the clinic for treatment. On admission the child was very dyspneic, with marked retraction at the suprasternal notch, and was completely aphonic. Dr. H. C. Carpenter noted on physical examination that the dyspnea was both inspiratory and expiratory. *x*-Ray examination of the chest as reported by Dr. Pancoast was negative, but the neck examination showed decided encroachment on the lumen of the upper trachea and larynx by a structure of soft tissue density. On account of the urgent dyspnea low tracheotomy was performed under local anesthesia. Dyspnea was entirely relieved, and two weeks after tracheotomy direct laryngoscopic examination was made, and large papillomatous masses were removed from the larynx. Following the scalping off of the papillomata the child was able to get air through the mouth with much less difficulty. The recurring papillomatous masses were scalped off by direct laryngoscopy, without anesthesia, at weekly intervals. At the end of six months of treatment there was only very slight recurrence of papillomata. The child had developed a hoarse voice and was getting air freely through the larynx; a partial cork was then inserted in the tracheotomy tube, the treatments being continued. At the end of nine months from the time of admission he was sent home under the care of the family physician, wearing his tracheotomy tube. Now at the end of six months' test period he has returned to the clinic, and on direct

laryngoscopic and bronchoscopic examination we find that the larynx is normal and entirely free of papillomata, but the bronchoscope shows in the trachea several papillomatous masses. Although these masses are not obstructive, we do not feel that it would be best to decannulate the patient at this time. We will send him home wearing the tracheotomy tube completely corked, so that he is breathing entirely through his larynx, and we will have him return at the end of another six months' period. If in that time the trachea and larynx are free of papillomata, he will be decannulated.

This case illustrates Dr. Jackson's method of treating papillomata of the larynx in children. Recurrent papillomata is a self-limited disease. Where there is marked dyspnea, low tracheotomy is done as the first step in treatment. This puts the larynx at rest and makes the patient safe from urgent dyspnea and asphyxiation. The papillomata are then scalped off so as to keep the larynx open. There is no local application of caustics or other medication, and great care is taken not to injure the larynx in the scalping off of the papillomata. Ultimately the growths cease to recur and the child has a normal larynx, as you see in this case. The time required for the cure of the patient varies, in some cases after eight or ten treatments complete cure has resulted. This patient has required much longer than the average period of treatment. We have no fear of difficulty in decannulation, as you see that he has a low tracheotomy. He now has a normal larynx and a normal voice.

CASE V. PAPILLOMATA OF THE LARYNX

This child, now six years of age, also had recurrent papillomata of the larynx following an attack of diphtheria when he was two years of age. Low tracheotomy was done and the papillomatous masses were scalped off. After several removals it was decided to apply radium. Two radium applications were made, and following this there was still found abundant papillomata in the larynx and pharynx. The child developed considerable fever and inflammatory reaction in the larynx, and after the subsidence of the acute symptoms he was unable to get any air through his

mouth. It was observed that he lost his voice entirely after the second radium application. When the child was admitted to the clinic direct laryngoscopy showed papillomatous masses completely filling the larynx on the postpharyngeal wall and around the base of the tongue. We were unable to find any opening through the larynx. Removal of the tracheotomy tube showed the upper trachea filled with papillomatous masses. The child was kept under observation and an attempt was made to restore the airway through the larynx by laryngostomy. On opening the larynx from in front it was found that there was complete obliteration of the airway through the cricoid and upper tracheal rings. The complete ring of cricoid cartilage was represented by a small island of cartilage, which was all that remained after the perichondritis following the use of radium. Without the supporting cricoid and upper tracheal rings we were unable to maintain an airway through the larynx and we have allowed the laryngostomy opening to close. There is, however, a large fistula in the trachea which will make it very much safer for the child if anything should happen to block the tracheotomy tube temporarily. We should like you to contrast this patient with the first. Here we see the effect of radium on papillomata of the larynx in the child. Sufficient radium was used to destroy the tender cartilages of the larynx, and we see papillomata recurring in the larynx where there is any remaining lumen. The sad inference is self-evident. The use of radium in this case was not only ineffective, but has destroyed the child's larynx. We have seen coming to the clinic many such cases as this. This is not an isolated case.

CASE VI. PAPILLOMATA OF THE LARYNX

This little girl first came under observation in the clinic when she was two years of age. She is now seven. When admitted to the clinic she was aphonic and urgently dyspneic. Dr. Jackson's method was carried out. Low tracheotomy was done, papillomata were scalped from the larynx at weekly intervals. She was decannulated two years after her admission to the clinic, and for a period of three years has been without her tracheotomy tube.

You will note that there is very little scarring in her neck, and that the fistula has closed spontaneously. Mirror examination of the larynx shows it to be normal and free of papillomata. She has a normal voice and is a normal healthy child.

CASE VII. CHRONIC POSTDIPHTHERITIC LARYNGEAL STENOSIS

This child, four years of age, developed laryngeal diphtheria when two and a half years old. Her voice and breathing through

Fig. 23.—Case VII. Photograph of a child four years of age, showing laryngostomy fistula and the open trough through the larynx at the point of previous postdiphtheritic stenosis. The wound is completely epithelialized and ample airway through the mouth has been established.

the larynx had been normal up to that time, indicating a normal larynx. She was intubated over a period of four weeks, the tube

was coughed out repeatedly, the patient becoming blue, and finally tracheotomy was done in emergency. After wearing the tracheotomy tube for a period of three months an effort was made to decannulate her, but practically no air passed through the mouth, and she was referred to the clinic for examination and treatment four months after the tracheotomy.

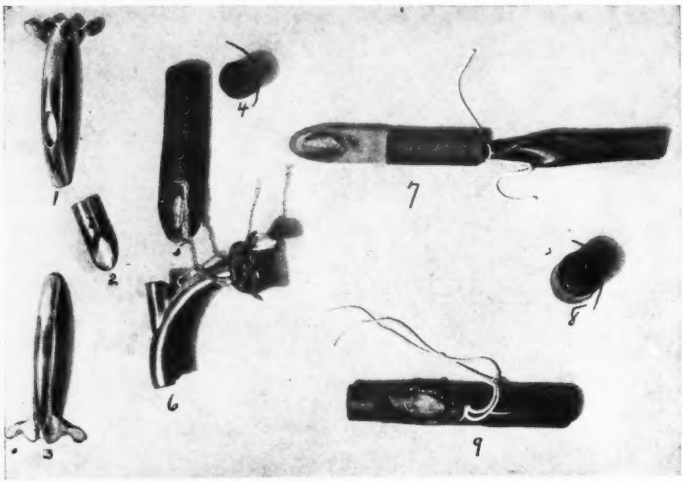

Fig. 24.—Case VII. Author's laryngostomy apparatus as used in treatment of this patient. 1, Open inner cannula. 2, Collar for attaching rubber dilating unit. 3, Closed inner cannula. 4. Open end of (5) cigarette drain rubber covered dilating tube. 6, Laryngostomy cannula of the author. 7, Extra thicknesses of cigarette drain cover added to tubing to increase size, and string tied around cigarette drain cover before it is pulled over to close the upper end. 8, Closed end of finger-cot tube (9). Closed cannula (3) is used for closed tube (9). Open cannula (1) is used for open tube (5).

On admission direct laryngoscopic examination showed a subglottic stenosis of the larynx, fibrous in character, the lumen through the subglottic area being about 1 mm. The tracheotomy tube was through the cricoid level of the larynx. The question as to the method of treatment was decided by retrograde examination by the retrograde laryngoscope, through the tracheotomy fistula. The fibrous tissue was so extensive that it was not

thought a suitable case for low tracheotomy and bouginage, but one on which a laryngostomy should be done. Laryngostomy was done by the Jackson technic; the postoperative course was uneventful and the wound including the trough through the larynx is now well epithelialized, and, as you see, there is an ample airway through the larynx in the region of the former stenosis (Fig. 23). The laryngostomy apparatus that we are using is the Tucker modification of the Jackson apparatus. The dilating unit is made of a rubber tube covered with Penrose drain (Fig. 24). This makes the tube perfectly smooth and we can increase the size by adding an extra thickness of Penrose drain. The wound is watched very carefully for points of excessive pressure and the pressure is relieved by grinding down the rubber core of the dilating unit with an emery wheel and recovering the Penrose drain. This apparatus will be worn for a period of about four months, and after we have attained sufficient dilatation and the patient breathes well through the mouth the wound will be closed by means of adhesive plaster during a test period of several months. Then the laryngeal fistula in the neck will be closed by Nassau's method for plastic closure.

This method of treatment extends over a period of at least one year, but in the end the airway is normal and the patient develops a good voice.

CASE VIII. STENOSIS OF THE LARYNX

This child, seven years of age, had a normal larynx up to the age of two years, when she developed diphtheria. She was intubated over a period of three months. Examination at that time showed papillomata of the larynx. The intubation tube was removed and tracheotomy was done. On admission she had developed a buccal voice, and when the tracheotomy tube was *in situ* and closed no air passed through the mouth. On removal of the tube a fair amount of air passed through the larynx and when the child cried a tone was produced by the vibration of the cords.

Direct laryngoscopic and bronchoscopic examination of the larynx from above showed the stenosis to be subglottic. There was present good motility of the arytenoids. The lumen of the

glottis admitted a 4-mm. bronchoscope when the tracheotomy tube was removed. The tracheotomy tube was through the larynx at the level of the cricoid. No papillomata were seen. In view of the large lumen through the glottis it was decided to do a low tracheotomy, and treat the larynx by peroral bouginage. You will note that after removal of the tracheotomy tube, which is now placed low, a No. 24 F. bougie passes readily through the larynx. The bouginage is carried out at weekly intervals without anesthesia.

This case offers very good hopes for cure by bouginage since the tracheotomy tube has been placed low. Note that the child has a good voice now when we close the tracheotomy tube with the finger.

As the dilatation progresses we will cork the cannula; at first partially, and then fully, and finally, when the child breathes under all conditions through the mouth with a full cork for a period of several months, the tracheotomy tube will be removed and the tracheotomy opening allowed to close; this usually occurs spontaneously. The larynx will be examined directly with a bronchoscope from time to time as the treatment progresses.

In the treatment of chronic stenosis we must be content to dilate the larynx gradually and slowly either by means of bouginage or apparatus. Rapid, forcible dilatation will defeat our purpose by setting up inflammatory reaction and perichondritis. In children normal growth of the larynx is a favorable factor.

These 2 cases are typical of postdiphtheritic stenosis or so-called "chronic tube cases."

CASE IX. CICATRICIAL STENOSIS OF THE ESOPHAGUS FOLLOWING LYE BURNS

This child, five years of age, swallowed household lye two months before his admission to the clinic. Examination on admission showed him to be well developed and well nourished, able to swallow liquids without much trouble; solid foods were regurgitated. Esophagoscopic examination without anesthesia showed marked dilatation of the upper thoracic esophagus, with a web-like stenosis having a lumen of about 2 mm. at a point 16

cm. from the upper teeth. There was no ulceration noted. Diagnosis was made of cicatricial stricture of the midthoracic esophagus with proximal dilatation. Peroral esophagoscopic bouginage was carried out, using the steel-stemmed filiform bougies of Jackson by sight. After four treatments the stricture was suffi-

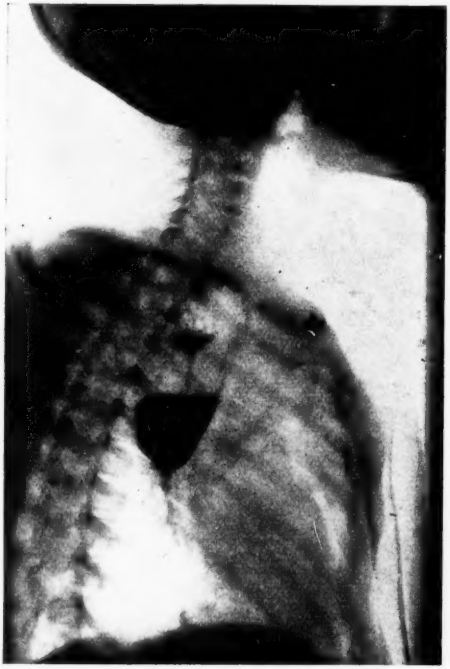

Fig. 25.—Case IX. Roentgenogram of chest showing strictured esophagus with proximal dilatation, filled with bismuth, before retrograde treatment.

ciently dilated to admit the passage of a 5-mm. esophagoscope into the stomach. Further dilatation was carried out esophagoscopically by sight and at the present time a 7-mm. esophagoscope passes into the stomach without resistance. The stricture is cured and the child will be kept under observation for a period of at least a year and an occasional esophagoscopic ex-

amination will be made to determine if there is any tendency to recurrence of the stricture. This case represents a mild type

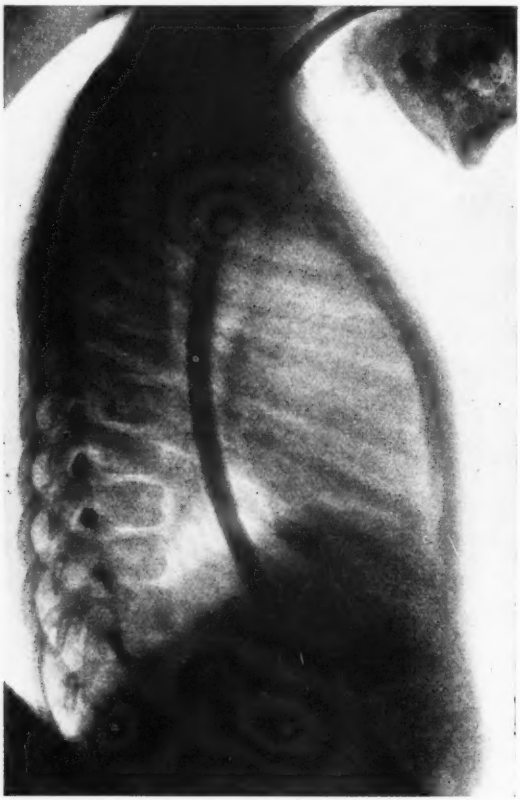

Fig. 26.—Case IX. Roentgenogram showing the Tucker retrograde bougie through the strictured esophagus. Note that all strictured levels are being dilated when the bougie is in position in the esophagus. Bougies were carried upward through the esophagus in gradual increasing sizes over a period of one year, at which time the stricture was cured.

of cicatricial stricture and responds quickly and safely to peroral esophagoscopic bouginage.

CASE X. STRICTURE OF THE ESOPHAGUS

This little girl, six years old, when three years of age drank a spoonful of a solution of lye which the mother had been using to make soap, the child thinking it was milk. The lye can was not labeled "Poison," and the mother thoughtlessly left the solution in the reach of the child. The child recovered from the immediate effects of the burn, but gradual increasing difficulty in swallowing developed, and at the end of four months became so severe that Roentgen-ray examination was made, and it was found that there was a long tight stricture involving the lower third of the thoracic esophagus with marked proximal dilatation. The child had lost considerable weight and was urgently in need of fluids, so gastrostomy was done by Dr. Outland, of Kansas City. Following the gastrostomy the child's general condition showed rapid improvement and the child was referred to our clinic for treatment.

On admission the child's general condition was good. All foods, including liquids, were regurgitated. Feeding was carried out entirely by tube. The child was given only water by mouth. Esophagoscopic examination confirmed the Roentgen-ray findings, and it was decided that this patient could best be treated by retrograde dilatation, using the Tucker retrograde bougie in increasing sizes. In the first step in this method of treatment, namely, the stringing of the esophagus, the child after two weeks' trial was *unable* to swallow a fine silk thread and a retrograde esophagoscope was passed through the gastrostomy wound upward to the point of stricture, and the smallest sized bougie was passed by sight through the esophagoscope into the strictured lumen. This gave sufficient dilatation to enable the patient to swallow water. She then swallowed a fine twisted silk thread, the upper end remaining through the nasopharynx and anterior nares, the lower end being brought out through the gastrostomy wound. To this thread was attached a larger sized silk thread that was pulled upward through the esophagus and used as the continuous string for carrying out the retrograde treatment. Dilatations progressed very slowly, as it was found that the stricture was extremely resistant. The bougie sizes were not stepped up until it

was found the size in use went through without resistance. Retrograde treatment has been continued at weekly intervals over a period of six months. When the dilatation reached the size of No. 18 F., food was given by mouth, all food being passed through a fine sieve so as to prevent the lodgment of masses in the esophagus. The gastrostomy tube was kept *in situ*. At the present time a No. 30 F. bougie, the largest size, comes through without resistance and the child can swallow all well-masticated food. The gastrostomy tube had been kept in the wound to maintain the fistula in case of emergency, should any solid food lodge in the esophagus. Further dilatation will be carried out by passing of esophagoscopes in increasing sizes up to 7 mm. and dilatation aided as necessary by steel-stemmed filiform bougies of Jackson. When the esophagus is dilated up to the normal caliber the child will be given a test period of at least a year, the gastrostomy tube being allowed to remain in the fistula, being changed regularly of course, and, if at the end of the test period esophagoscopic examination shows the esophagus to be normal, the tube will be removed and the fistula allowed to close. In the majority of instances the fistula closes spontaneously, but if it does not the surgeon will do a plastic closure of the opening.

We will now show you our method of retrograde dilatation by pulling through the largest size Tucker retrograde bougie. The child has experienced very little discomfort during the procedure. Many of these children are treated as out-patients and attend school wearing the string through the anterior nares and over the ear as you saw in this little girl. This method of treatment has the advantage of absolute safety if reasonable caution is used in stepping up the bougie sizes. The pulling upward of the bougie through the esophagus means that all stricture levels are dilated at each treatment, and in cases where there are multiple strictures the time required for cure is very much shortened. (See Figs. 25, 26.)

CLINIC OF DR. T. GRIER MILLER

UNIVERSITY HOSPITAL

THE SIGNIFICANCE OF THE MEDICAL SUPERVISION OF EMPLOYEES IN SMALLER BUSINESS ORGANIZATIONS

THE value of a medical department in the organization of large industrial and public service corporations is now fully appreciated, and the personnel of such a department commonly consists of a well-trained corps of full-time doctors, nurses, and assistants. The equipment may be only that of a dispensary, but not infrequently a well-appointed hospital is included. The original purpose in such an organization was to care for the physically injured, and so a surgeon usually has been the officer-in-charge, but as the idea has developed other equally important medical functions have been added and now the work is of as much appeal to the medical man as the operator. The various functions, as at present conceived, may be summarized as follows: (1) To care for the sick as well as the injured; (2) to eliminate the physically unfit, and (3) to preserve the health of the individual employee by (*a*) correcting remediable physical defects, (*b*) minimizing specific health hazards, and (*c*) supervising hygienic conditions. Laws have been enacted which place an obligation upon the employer in respect to some of these matters, and yet there are purely economic reasons which justify them. This is suggested by the fact that many organizations have gone far beyond the legal requirements in the perfection of their medical departments.

The desirability of such medical service in the smaller business concerns, such as stores, banks, and the lesser industries, is not so obvious, since in these surgical injuries are rare and special health

hazards are not common. Yet, after all, these are minor considerations in many of the large corporations, and the average industrial physician today is probably concerned primarily with just such individual disease problems as present themselves to the civilian doctor. These must be essentially the same no matter what the size of the organization. The reason this type of work has not been taken up in connection with the smaller groups of workers is doubtless, in part at least, a practical one, and resolves itself into a difficulty in organization so that the per capita expense will not be excessive. My object in this presentation is to point out the way in which this problem has been faced by one of the smaller banks of Philadelphia, and to show its value not only to the institution itself and its employees but also to the physician concerned.

The experience detailed has been an incidental personal one, covering a period of five years, and it is recognized that it may not represent an ideal system and that it may not be applicable to all similar concerns, even of as small size; but it is hoped merely that it may serve as an illustration of what can be done and encourage other institutions and physicians to give it a trial.

In the fall of 1921 this bank asked me to examine its personnel with the dual idea of rendering a service gratis to them, in line with the current thought of aiding the welfare of employees, and at the same time hoping that some benefit might accrue to the organization itself. It was the original intention to have a medical man come to the bank at certain fixed times, make physical examinations of those desiring it, and offer such advice and give such treatment as seemed appropriate. This was not feasible from my viewpoint, however, and the countersuggestion of having the employees come to my office individually and by prearranged appointment was agreed to. In response to the opportunity afforded them, most of the approximately 100 workers were given careful medical study within the first six months and since then all applicants for a position at that bank, mostly young boys and girls, have received a similar physical investigation before being accepted for duty. In all, 165 individuals, 113 men and boys and 52 women and girls, have been so studied.

The routine procedure has been to secure, within the half-hour allotted to each person, in addition to his name, age, and sex, the name and address of his family physician and a careful family, social, and medical history; to make a thorough-going physical examination; to take the weight; to do a urinalysis; to determine the blood-pressure, and, where indicated, to have a Wassermann test done and to secure examinations by workers in special medical lines. Thus the study has been quite comparable to that made of ordinary private patients. It has in no sense been as exhaustive as one would make of patients in a hospital, and this must be remembered in judging the results.

Upon making the original study of each individual the findings were carefully explained to him and a written report was sent to a specified officer of the bank who kept it concealed from all others. In the instance of an applicant for a position, a recommendation was made as to acceptance or rejection purely on the basis of his physical condition. Only those with irremediable and progressive disease, such as in one instance a primary anemia, were considered improper risks; others with less serious lesions, such as diseased tonsils, oral sepsis, defective hearts, and albuminuria, were not turned down, but the physical status was explained, leaving it to the bank officer to accept or reject. If accepted, it was recommended that they have the remediable defects, such as infected tonsils, oral sepsis, refractive error or what not promptly corrected, or that they be accepted tentatively for six months with the understanding that they be re-examined at the end of that time. For those found normal no re-examination was specified, but the bank at all times permitted them to ask for such restudy.

Furthermore, it was understood that any employee developing an illness could request examination and treatment by the company's physician or could see his own family doctor. Under all circumstances an effort was made to co-operate with the patient's family physician. When recommendations for special treatment were made it was always suggested that the family physician be consulted, and such physicians were not infrequently advised directly of the advice given. In some instances it has

happened that I have been asked to see an employee with his own physician.

Another service considered by the bank as belonging to this department was the investigation of unexplained absences, and this it has been possible in several instances to do by having my secretary make a visit to the home. When such an individual has been found sick inquiry has been made as to the physician in charge and he has been consulted as to the nature of the trouble.

Thus the functions assumed by me in this service, in addition to the original examination of all the personnel, have been (1) to examine all candidates for positions, (2) to report on their physical status and acceptability from that viewpoint, (3) to advise special therapeutic procedures to increase the chances of good health, (4) to care for illness when no family physician was available, (5) to investigate causes of absence which it seemed probable were due to illness, and (6) to consult with the family physician when requested to do so. Although these responsibilities have been accepted in the midst of other more important duties and have necessarily been neglected to a certain extent, it is felt that some of the results and a brief discussion of them are worthy of record.

In the first place, let us see whether or not the bank itself has benefited. Its interest, we may assume, is only of a business nature, though, as a matter of fact, the attitude of the officers in this particular institution has seemed truly philanthropic. The latter is not, however, to be considered here.

A result that can be expressed in figures is contained in the following table submitted to me by an officer of the bank:

Year.	Total number of employees.	Number absent one or more days.	Total days lost.
1921	78	61	827
1922	82	62	1272
1923	90	65	429
1924	93	51	552
1925	83	54	558

The total number of employees for each year in this table includes only those on whom time-card records were kept and is

not quite complete. Some of the days lost were due to conditions other than illness, but this number was small. The high number of days lost during 1922, my first year, was due chiefly to the continuous absence of two women in whom I found evidence of active pulmonary tuberculosis and who were carried on the books during their entire illness. No other case of active tuberculosis has occurred in the five years. It will be noted that the total days lost in the last three years were substantially reduced. It is of interest, too, that the girls and women lost about three times as many days as the boys and men. Some of these absences were due to menstrual conditions which cannot be entirely eliminated.

It is obvious that the days lost will vary from year to year and are subject to increase in times of epidemics, such as the influenza one of 1918–19, but no such conditions have to be considered within the period of time under consideration.

If, therefore, we assume that the days lost in 1921 (827) represent an average for the period before this system was adopted, omit the figures for 1922, which are high because of our own discovery of tuberculosis cases which should have been detected beforehand or never accepted for duty, and take the average for the remaining three years (513), we find an annual decrease of 312 days, and this occurred in spite of the fact that the number of employees on whom time cards were kept had slightly increased. At $3 per day this means an actual saving to the bank of $936 yearly.

But this has not been the chief advantage of the plan from the administrative standpoint, according to one of the officers, who emphasizes in a letter to me the value of its psychologic effect. This is difficult to state concretely, but it doubtless means not only that the employees have reacted favorably to such interest showed in them by their employers and have, in consequence, given more satisfactory and more continuous service, but also that the officers themselves have felt a certain satisfaction in providing facilities designed to increase the welfare of their workers and also in having available the machinery for handling such medical emergencies as might arise.

Such a medical emergency occurred about one year ago when a number of cases of smallpox appeared in the city and the Board of Health urged every one to be vaccinated or revaccinated against this disease. When consulted about this I secured a medical associate and a trained nurse, and together we went to the bank and vaccinated the entire personnel on a single morning.

In the second place, the employees have been given a sense of protection and a greater confidence in themselves. Many of them have come for examination with fears about trivial symptoms which could be allayed only by medical opinion following upon careful study. Many neuroses have their origin in such mental states, and are more easily prevented than cured. Some of these persons might otherwise have gone to their own physicians, but others, on account of the expense and through ignorance, would have waited for more advanced symptoms, when they could not have been so easily relieved.

Furthermore, actual diseased conditions have been found which, being corrected, have protected against serious conditions in later life. No argument is needed to prove the benefits of eradicating various focal infections: septic tonsils, diseased teeth, and infected sinuses. Of the group studied to date, 37 had definite septic conditions of the sinuses or tonsils, and 32, of the teeth. Not all of these have had their defects corrected, but many have, and the others at least are aware of their abnormalities, and will be more inclined toward the proper therapeutic measures should secondary conditions begin to develop.

Refractive errors have been suspected in certain instances, and the individuals having these have been referred to competent ophthalmologists rather than to optometrists, and thus again a condition leading to eye-strain and its attendant ills has been prevented.

Perhaps of equal importance to the employee has been general advice about hygienic matters: keeping the teeth clean, frequent bathing, regular forms of exercise, and dietary matters. Suggestions along such lines have always been taken kindly, and doubtless have been heeded more frequently when given by a strange doctor having an official connection with their employer

than if given by a parent, a social worker, or perhaps even the family physician.

Finally, and in the third place, of what value is such service to the physician himself? Because it is least pleasant, and yet very necessary, let us consider the financial side of this question first. The remuneration for such work is usually on a salary basis, but because such an arrangement tends to focus attention on the job as a whole rather than on the individuals concerned, because it is not in keeping with common professional methods and because the amount of work could not be foretold, and depended largely upon my own interest in it, I preferred to make my charges strictly on the basis of work done. A scale of prices was agreed upon that allowed reasonable compensation, but naturally less than would be expected from ordinary private patients. This aspect of the matter can be varied to meet different circumstances, but I have no hesitation in saying that little difficulty will be encountered in securing adequate compensation from business organizations for the type of medical service rendered.

If this were all that could be said for the physician, however, the plan would make no real appeal to the ambitious clinician who is always more concerned about increasing his knowledge and experience than making money. But in this respect also I have found this work well worth while. The mere examination of healthy young boys and girls, if carefully done, leads to a better appreciation of the normal, and gives one a better point of view about the abnormal. This is particularly true when it is possible to see these individuals regularly from year to year and note developments, even normal ones.

Furthermore, though all were presumably normal, the majority of these individuals were not. Only 37 of my series of 165 presented no definite variations from the normal and were classified as without evident disease. The others presented a remarkable group of pathologic conditions: digestive, circulatory, renal, and nervous, in addition to the focal infections already referred to. Not all of them could be satisfactorily studied or diagnosed. It may be instructive in this connection to present a few of the

cases that have been encountered and to indicate how they have been handled.

(1) A woman of forty-five years, a widow with one child, complained only of headaches, some gas in the bowels when nervous, and of pain in the abdomen when pushed in her work. On further questioning she admitted some menstrual irregularities and nocturia. She stated that her husband had died of blood poisoning nine years before and that her only child (of fourteen years) was living and well. There were no important physical findings, though the second aortic heart sound was clearly accentuated and her blood-pressure was 165/100. Urine was negative. It was suspected at first that her symptoms were due to oncoming menopause and strain in her work plus caring for her child and an invalid mother. Six months later, while on her way to work, she became dizzy, had a peculiar sensation in the left arm and leg, difficulty in walking, became nauseated, and vomited. Paresis of left side of body was found, a positive Babinski sign, and blood-pressure of 170/100. A visit to her home revealed a mentally defective child with an interstitial keratitis, and further questioning disclosed a story of syphilitic infection soon after marriage. Wassermann was strongly positive. Treatment with mercury and salvarsan brought about considerable improvement, and now, after more than four years, she is still steadily at work, though some spasticity of the left leg persists.

Without the discovery of a syphilitic basis for this patient's cerebral attack, which might have been missed but for the visit to her home, one could not have been hopeful of the outcome, but in view of that the bank was advised, after three months, to take her back on a half-day basis, and she was soon able to resume her full work and has given satisfactory service. But for the attitude and tolerance of the employers in this instance, incident to the encouragement which I could give them, she would probably have lost her position, have become discouraged, and would finally have sought another and doubtless less remunerative position. The bank also has benefited by her continued services, and to me she has been a most instructive patient.

(2) A young woman, aged twenty-eight, while at work at her desk in the bank on October 10, 1921, was seized suddenly with a feeling of faintness and tingling throughout the body. Her heart thumped violently and was very rapid. This attack lasted but a few minutes, but there were several recurrences before a physician could get to her. A history was then obtained of chorea at ten years of age, of typhoid fever at thirteen, and of dyspnea and palpitations on undue exertion after that time. During the month preceding her immediate attack she had suffered from a severe cold with cough. She had not pre-

viously received a physical examination and did not know that she had any heart disease. Examination readily disclosed a typical well-developed mitral stenosis with beginning decompensation (the latter precipitated by her recent cold). All special examinations were negative. After a rest in a hospital for ten days and at home for several months her condition was such as to justify resumption of her work, beginning with half-time. Instructions were given as to the nature of her trouble, the danger of neglecting minor infections, and of exposing herself to physical and mental strains; and now, after four years, she is still at work, and has required only brief periods of rest for slight colds and the use of mild nerve sedatives from time to time.

Here again is a most interesting case that has been saved to herself and her employer by medical supervision. The results have justified the expense to the bank of her hospitalization and medical care, and surely observation of her case over almost five years has meant more to me than could the study of many cases of mitral stenosis over short periods of time in hospital wards.

(3) A man aged thirty-five, married, and having 2 healthy children, was originally examined and found normal on March 7, 1922. On October 10, 1922, he came to me with what seemed to be an ordinary follicular tonsillitis. Six days later, to my surprise, he had larger patches on his tonsils and a thin pearly layer of exudate; also his anterior cervical lymph-glands were much enlarged. A smear was negative for diphtheria or other special organisms. Dr. George Fetterolf was asked to see him, and he also was puzzled, but suggested among other things the possibility of syphilis. A Wassermann test was strongly positive, and the tonsillar lesions and adenopathy readily cleared up under arsphenamin locally and intravenously.

In this instance there existed the possibility of transmission of a serious disease not only to members of the patient's family, but to his fellow-workers, as well as the development of tertiary syphilitic lesions in later life, had his throat infection not been properly diagnosed and treated.

(4) A man of thirty-five years, single, received his first examination on November 14, 1925, gave a negative history for infections of any kind, and had never indulged in strenuous physical work or play. His brachial arteries were tortuous and markedly beaded. Heart was negative. Blood-pressure was 135/80. Urinalysis was negative. On account of the marked degree of arteriosclerosis at such an early age I asked to see him again, and a review of the case on April 6, 1926, revealed like conditions. Again the urine examination was negative, the blood-pressure was 130/80, and the heart showed only a very slight systolic blow at the apex. Wassermann was negative. Eye-grounds showed slight arteriosclerosis.

This patient's record is presented on account of the isolated finding of arteriosclerosis at such an early age, and it will be of extreme interest to follow his case from year to year, a thing that would rarely be possible in a hospital dispensary, and never in a hospital ward.

(5) R. G., aged sixteen, who had just finished his second year in high school, presented himself for examination as an applicant on January 6, 1923. He had no symptoms and had never been sick except for an occasional sore throat, but admitted that he had never been quite the equal of his fellows in an athletic way. He showed a little circumocular edema, was pigeon breasted, and had a slight dorsal scoliosis, suspicious looking tonsils, a general adenopathy, and a large mass in his right upper abdomen which I took to be a ptosed liver or kidney. His urine showed a cloud of albumin with a specific gravity of 1.025, but no casts. I suspected a chronic nephritis, and suggested that he might not be able to give satisfactory continuous service. He was accepted for a probation period, however, and, on October 1, 1923, he again came to me, having a much better general appearance, having less certain edema about the face, and somewhat less albuminuria. A tonsillectomy was suggested, but not performed. Since then I have seen him on a number of occasions, twice for acute tonsillar infections and once for an acute bursitis, and he always had some albumin in his urine. On my last examination (April 12, 1926) his urine contained a heavy trace of albumin and an occasional hyaline cast, his blood-pressure was 100/80, he looked thin, and complained that he could not gain weight. His tonsils appeared definitely septic and I strongly urged that they be removed.

Here it seems probable that a chronic nephritis is present and that the tonsils are at least a factor in the etiology. Their removal should doubtless have been insisted upon earlier, but I was not convinced of their septic nature until the last examination.

(6) C. R. B., aged fourteen, had had pneumonia three years before I examined him on July 2, 1923, but otherwise had always been without symptoms. His weight was 106 pounds, he was thin and a little pallid, nearly fainted on examination, had facial acne, a slight left-sided dorsolumbar curvature, a slightly widened heart with a systolic murmur at base and apex, and large septic tonsils. His urine contained a heavy cloud of albumin and many light and dark granular casts. Blood-pressure was 110/50, hemoglobin was 85 per cent., and phthalein test was normal. I advised rejection of this boy for the time being on the basis of a nephritis, and urged tonsillectomy. His mother then brought him to me with a report from a "biochemical laboratory" showing no albuminuria, but still I found a distinct trace, and his own doctor admitted to me that he had found some albumin.

Tonsillectomy was refused, but I agreed to his tentative acceptance for six months. At the end of that time his weight had increased to 123½ pounds, he seemed in much better general condition, but the tonsils were still decidedly septic, and the urine still contained a trace of albumin and some casts. I again urged tonsillectomy, but his own physician opposed this. I did not see him again for more than two years (April 12, 1926), and then found a light cloud of albumin and many granular casts. The tonsils were as before, and now I believe he will undergo the operation.

This case indicates the difficulties sometimes encountered in getting discovered foci of infection eradicated, but in no sense discourages one from making the effort. His nephritis is perhaps already too far advanced to be completely cured, but added insults from the tonsils may yet be prevented.

(7) K. G., aged eighteen, was first seen as a candidate for a position on February 2, 1926, and gave a medical history of only measles and chickenpox, with a very occasional cold. He had graduated at high school and had always indulged in horseback riding for his exercise. His appearance was that of a normal young man, but, to my surprise, he had a blood-pressure of 160/75 and his second aortic heart sound was clearly accentuated. No aortic diastolic murmur was detected. His face was quite ruddy, suggestive of erythremia, but the red cells numbered only 4,800,000 and his hemoglobin was 90 per cent. His conjunctivæ were a little injected, as was also his throat, but the tonsils were not septic. His right kidney was very low (easily held down during the whole respiratory phase) and his urine contained a cloud of albumin with many hyaline casts. His family physician has since found both the elevated blood-pressure and the albuminuria. On a recent examination (when he had not ridden horseback for two days) there was no albumin in the urine, but the pressure was still 150/80.

One is lead to suspect that his almost daily horseback riding has been a factor in displacing this boy's right kidney and so leading to circulatory disturbance of that organ which accounts for the albuminuria, but it is not so certain that the elevated blood-pressure can be explained in this way.

(8) R. S. G., aged fifteen, was examined on June 26, 1924, and gave a history of repeated tonsillar attacks previous to a tonsillectomy done in 1920. Examination revealed evidence of a mitral regurgitation and a heavy trace of albumin in his urine. No focal infections could be found. He was tall, thin, somewhat pallid, and weighed only 87 pounds. It was recommended that he be accepted for duty, and some advice as to outdoor exercise was given. Six months later he was in much better general condition, had gained 5 pounds

in weight, the heart murmur had distinctly decreased, and the urine showed only a mere trace of the albumin.

Several such cardiac cases have been seen and have showed improvement while under observation.

These selected cases are presented not particularly to emphasize any unusual clinical conditions, but to suggest the wealth of material that is available for study in medical work of this kind. When it is considered that such experience can be obtained in work that is at the same time remunerative and that can be handled in one's office and entirely at one's convenience, without giving extra time to it, it should make an appeal to the younger medical men connected with our hospitals who have not as yet developed much private practice, but who are well trained for just such work.

I have tried, therefore, to point out the value of the medical supervision of employees in smaller business organizations by presenting a personal experience in such work, and have detailed some of the advantages that may result to the employer, the employee, and the physician himself.

CLINIC OF DR. CHARLES C. WOLFERTH

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ON THE TREATMENT OF ABNORMAL CARDIAC RATES AND RHYTHMS

ABNORMAL cardiac rates and rhythms are expressions of underlying disturbances which affect the heart. They are symptoms, not diseases—sometimes unimportant symptoms requiring no treatment, sometimes dominating the clinical picture and imperatively demanding treatment. One's ultimate goal in treatment should never be merely the successful management of the disturbed mechanism, but discovery and attention to the fundamental cause of disturbance. A discussion of cardiac therapy which does not include consideration of etiology, although not altogether useless, is comparatively ineffective.

Simple Tachycardia.—A consideration of simple tachycardia at once leads to emphasis on the validity of the statements just made. Tachycardia is, far and away, the most frequent and most important disturbance of the heart action. Every physician, no matter how inexperienced, turns immediately, on encountering tachycardia, to reflections as to its cause, since it is obvious to everyone that tachycardia is a symptomatic disturbance that may occur in a perfectly healthy heart.

In the entire domain of medicine there is probably no more urgent need for an effective drug than in the treatment of simple tachycardia. I am sure that countless lives now lost could be tided over crises of serious illness if we were but able to slow the cardiac rate and thus better conserve the strength of the heart.

Not infrequently, by effects exerted on the underlying cause of tachycardia, drugs are able to bring about slowing. Thus,

iodin in exophthalmic goiter, by abating the thyrotoxicosis, frequently brings about a marked fall in pulse rate. The slowing of the pulse in pneumonia which often follows morphin is to be attributed more to improvement of restlessness, cough, and general discomfort than to vagus stimulation. The decrease in rate after the use of epinephrin in a paroxysm of asthma is a conspicuous example of indirect effect, since the direct effect of epinephrin on the cardiac regulatory mechanism is to increase the rate.

If, however, we limit our discussion to those drugs capable of producing cardiac slowing by their direct action on the heart or the nervous control of the heart, none but the digitalis group warrants consideration. Others, such as physostigmin, strychnin, small doses of atropin, etc., may be shown under certain circumstances to produce cardiac slowing, but they are practically useless in cases urgently demanding this action.

Digitalis is used almost universally in the treatment of tachycardia. One notes its employment particularly by surgeons, many of whom resort to the dubious practice of administering it hypodermically after operations and, indeed, at other times. I have twice seen extensive cellulitis and death following digitalis injections in patients in whom recovery might otherwise have been expected.

What is the basis for the extensive use of digitalis in tachycardia? It would seem that any measure so widely employed must have merit. Doubtless its reputation for slowing the heart rests chiefly on its spectacular effect in slowing the ventricles in auricular fibrillation and flutter. The effect in fibrillation and flutter is produced by blocking transmission of a larger proportion of the impulses from the auricles during their journey through the junctional tissues. In the normally beating heart slowing is rarely produced by block in the junctional tissues unless a defect in conduction is already present. The amount of digitalis necessary to block the normal impulse in healthy junctional tissue usually exceeds the toxic dose. Thus ordinarily we have to rely on its effect in retarding the discharge of impulses from the sinus node. This effect is probably brought about purely through the vagus nerve, there being no reliable evidence

that digitalis in therapeutic doses influences directly the sinus node to produce slowing.

In children the vagus mechanism is more responsive than in adults, and marked effects in slowing the rapidly beating heart by digitalis may not infrequently be obtained if heavy dosage is employed. Sutherland, who has published some beautiful records showing this effect in postrheumatic tachycardia, points out nevertheless that the slowing does not occur if fever is present. I have frequently failed to slow the heart appreciably in the afebrile postrheumatic cases, even though digitalis was pushed to the limit of toleration. Not infrequently, however, the junctional tissues have been damaged at least temporarily by the infection, so that large dosage of digitalis will produce incomplete or even complete block. It is questionable if such a method of producing slowing is desirable.

In adults the treatment of simple tachycardia with digitalis is usually disappointing. There is no doubt that digitalis is capable of improving the circulation in some patients with normal mechanism and extreme heart failure. Many investigators have published data to establish this fact, and we have demonstrated it repeatedly under the most rigid control we were able to employ for very ill patients. In these patients with extreme heart failure improved by digitalis the cardiac rate, if originally rapid, sometimes falls. How much of this fall is a direct digitalis effect on the heart and how much an indirect effect resulting from a more efficient beat and improvement in the circulation is conjectural and a somewhat academic point. In an adult without failing circulation it is highly exceptional to obtain appreciable slowing of simple tachycardia from digitalis even though it be given to the point of producing nausea or vomiting. In the cases in which slowing does occur, the explanation has been advanced that it is due to an unusually responsive vagus mechanism.

For several years Dr. Rose and I have been making observations of the effects of digitalis on the heart in patients with hyperthyroidism. In spite of the responsiveness of the heart rate to changes in the intensity of the thyrotoxicosis as measured by the metabolic rate, we have been unable to demonstrate an ap-

preciable effect of digitalis in slowing these hearts, independent of changes in the metabolic rate.

Simple Bradycardia, Ventricular Escape, Auriculoventricular Rhythm.—It has frequently been stated that simple bradycardia with a rate under 40 is rare. While this statement is undoubtedly correct, an extremely slow sinus rate is masked, if it drops below the automatic rate of the node of Tawara, by the development of ventricular escape or auriculoventricular rhythm. Consequently, these forms of arhythmia, unless due to abnormally increased excitability in the node of Tawara and manifested by a comparatively rapid rate, owe their emergence to sinus bradycardia. As a rule, they can be abolished readily if desired by the simple expedient of increasing the sinus rate. The treatment of these arhythmias is, therefore, the same as that of simple bradycardia.

Although many patients with simple bradycardia have serious heart disease urgently demanding treatment, it is seldom that the bradycardia itself requires treatment. Occasionally, however, such symptoms as vertigo, weakness or exhaustion, and faintness may be largely contributed to by bradycardia.

While there are several drugs that will increase the heart rate, the clinical results obtained, at least so far as subjective symptoms are concerned, are mostly disappointing. The extreme bradycardias are usually found in patients with profound myocardial exhaustion. In such individuals the most important part of treatment is prolonged rest and other measures designed to help rebuild cardiac reserve. In those in whom increased vagus tone is a factor, particularly younger patients, the use of atropin in appropriate dosage may prevent fainting attacks. In the elderly caffein may be very helpful. In patients with low blood-pressure the new—at least new to this country—drug, ephedrin, deserves a trial, and in those with high pressure the nitrites may be of use. Bradycardia after an acute infection practically never requires treatment. Those cases due to hypothyroidism, inanition, and jaundice are best managed by treatment of the fundamental condition.

Sinus Arhythmia.—It is almost universally conceded that sinus arhythmia requires no treatment, but this rule, like most other good rules, has some possible exceptions. There is a well-defined clinical entity occasionally found in children and adolescents in which the outstanding features are exaggerated sinus arhythmia and fainting attacks. Unfortunately, not a few of these cases have been incorrectly diagnosed epilepsy. Most are relieved of their fainting attacks by a vigorous outdoor life with regular habits of eating and sleeping, and not too close application to study. Atropin will temporarily abolish the syndrome, but, as in the treatment of all forms of bradycardia, it is merely a temporary expedient and has no real curative effect.

Exaggerated sinus arhythmia with associated bradycardia is occasionally found immediately after exercise. It is analogous to the better known but rarer postexercise sino-auricular block. It is liable to be attended by violent palpitation. In such cases, in spite of lack of evidence of myocardial damage, it is probably wise to restrict severe exertion.

Sino-auricular heart-block, except as a temporary phenomenon after severe infections (especially diphtheria), digitalis administration, or immediately after exercise, is extremely rare. I have had opportunity to study only 1 case with long-continued sino-auricular block. This patient, a highly intelligent woman over fifty years old, states that she had noticed her arhythmia for at least twenty years. I have personally observed it, and made electrocardiograms over a period of four years. The arhythmia is unaffected by strychnin, bromids, or theobromin. It is decreased, but not abolished, by nitrites. Atropin, pushed to the physiologic limit, lessens the arhythmia, but does not completely abolish it. Digitalis increases the number of dropped beats. Exertion diminishes the arhythmia. It has been pretty thoroughly established in this patient that increased vagus action increases the arhythmia and decreased vagus action lessens it. It has frequently been noted that the arhythmia is much worse during periods of nervous exhaustion to which this patient is subject, and may almost entirely disappear with improvement in the state of the nervous apparatus.

Extrasystoles.—There is a disposition in some quarters to regard extrasystoles as of little if any significance. The clinician may not safely ignore them. Extrasystoles indicate that some portion of the heart muscle, however small, has been functionally altered from the normal. It is not without significance that extrasystolia is common—one might say almost universal—in clinically recognizable myocardial disease or exhausted states of the heart. On the other hand, it must be admitted that extrasystoles are often found also in hearts in which no other evidence of disease is detected. In fact, many life insurance companies, as a result of their experience, now issue standard policies on such risks. Nevertheless, the presence of extrasystoles should always constitute a challenge to determine their cause, and a complacent attitude toward them should be avoided until the various possibilities are exhausted.

The treatment of extrasystoles is concerned chiefly with a search for their precipitating causes. They may be excited by such diverse agencies as mental strain or worry, excessive use of tobacco or coffee, infected teeth or tonsils, gastric disorders or gall-bladder disease. Invariably a careful study of the cardiovascular apparatus is indicated. The attempt to remove the exciting factor has a deeper significance than the mere abolition of such a trivial disturbance of the heart action as extrasystolia. If these conditions cause extrasystoles, they probably also exert a deleterious although possibly undetected effect on the heart muscle.

Sometimes it is necessary to attempt suppression of extrasystoles by the use of drugs. Some persons, particularly those of a nervous temperament, are seriously annoyed by extrasystoles and cannot be persuaded to disregard them. So far as I know, these beats or the succeeding ones, which are those usually noted, are never actually painful, but these persons go about in a constant state of apprehension and are often kept awake or actually awakened by the skipping or thumping of the heart. A second but much rarer indication for the suppression of extrasystoles is found in the cases they serve as portals of entry for more profound disturbances of rhythm, such as paroxysmal tachycardia, auricular flutter, and fibrillation.

A great variety of drugs has been advocated in the treatment of extrasystoles. Caution is necessary in interpreting results of treatment because of the great variability of incidence of this arhythmia. Probably the most effective drug is atropin, which produces its effect chiefly if not entirely by accelerating the heart rate. Its side effects, however, in these nervous patients are liable to be more disagreeable than the extrasystoles, so that its use is seldom to be regarded as successful. Wenckebach strongly recommends strychnin, but I have seldom observed good results. Bromids are not infrequently helpful, particularly in the most nervous patients. Exceptionally digitalis is brilliantly successful, but usually fails, and may even increase the arhythmia. If none of these measures are effective, and it seems necessary to tide a patient over a temporary period, quinidin may be resorted to. It may seem absurd to employ so powerful a remedy as quinidin to treat so trivial a disturbance as extrasystolia, but in this age of tortured nervous systems it is sometimes highly useful. It is not always effective, but gives far better results than any other drug I have ever tried. The effective dosage is found by trial, but no more than 2 grams daily is given. It should be used only in the patients with a good myocardial reserve. Under these circumstances I have never seen untoward symptoms except occasional mild cinchonism.

Paroxysmal Tachycardia.—According to current opinion, paroxysmal tachycardia consists of a succession of extrasystoles. At any rate this condition is closely allied to extrasystolia, which is of importance in the treatment of paroxysmal tachycardia, since the statements made above with regard to search for and eradication of the exciting causes of extrasystoles also apply to paroxysmal tachycardia.

Vagus stimulation can be applied effectively to terminate paroxysmal tachycardia of auricular origin in approximately 50 per cent. of the cases. As might be expected, this method appears to be of no value in ventricular tachycardia.

The most effective methods of vagus stimulation appear to be direct pressure on the nerves in the neck or pressure downward and inward on the eyeballs. Other maneuvers occasionally

successful are: having the patient take a deep breath and hold it, rapidly swallow cold water, or lie with head down and legs up in the air. Patients occasionally discover unusual methods of suppressing paroxysms. These usually consist of the assumption of peculiar positions, methods of breathing, or straining. One patient recently in the wards here had learned the value of pressure in the neck through having put his hand there in the attempt to stop throbbing. Some days when attacks were frequent he kept himself pleasantly occupied stopping them.

If physical methods are unsuccessful in terminating a paroxysm, we usually allow it to continue until it terminates spontaneously. If the paroxysm seems to be lasting too long, quinidin given by mouth may help to terminate it. Certain European investigators have shown that intravenous injection of 0.5 gram quinin or quinidin is a highly effective method of terminating paroxysms, but this method is probably not without danger and should be reserved until the patient's condition is serious. Its chief value is probably in ventricular tachycardia in which paroxysms may threaten life. Auricular tachycardia rarely brings the patient to such desperate straits.

Quinidin has proved itself extremely valuable in the treatment of patients with rapidly recurring paroxysms. It is the only drug we possess which exerts a powerful effect in preventing the onset of paroxysms. The amount necessary to give to any patient must be learned by trial. Apparently as much as 2 grams in divided doses daily may be tolerated by some patients over periods of weeks or even longer without deleterious effects. In some patients quinidin to the limit of toleration does not prevent attacks.

Auricular Fibrillation.—It is sometimes stated that digitalis is almost a specific for auricular fibrillation. This statement is quite misleading. The principal action of digitalis is to slow the ventricular rate so that the heart is enabled to obtain more rest and consequently beat more efficiently. It does not tend to abolish fibrillation, nor does it influence the fundamental conditions that have so altered the functional state of the heart muscle as to make fibrillation possible. Specific treatment of auricular

fibrillation would have to be directed toward eradication of its cause. When the cause is hyperthyroidism, appropriate treatment of this condition may be brilliantly successful in abolishing fibrillation. In other conditions results are not so good. Success depends on how much restoration of muscle function can be accomplished.

It is necessary to consider the treatment of paroxysmal fibrillation separately from that of established or chronic fibrillation. No form of cardiac disorder illustrates more impressively the danger of focussing too narrowly on "cardiology." If attention is directed to the heart alone, treatment is at best a defensive or rear guard action. No group of patients require more careful general study than those with paroxysmal fibrillation or, indeed, any of the forms of paroxysmal rapid heart action. I could cite from our experience in the University Hospital more than a dozen patients in the last three or four years entirely relieved of these attacks by appropriate treatment of the thyroid, and other cases improved or entirely relieved by a suitable régime of life, proper care of the gastro-intestinal tract, or removal of badly infected tonsils. Other foci of infection also deserve consideration.

It must be admitted, however, that not infrequently our efforts to remove the cause of paroxysmal fibrillation are doomed to failure. If attacks are frequent and burdensome, it may be necessary to attempt their suppression by drug therapy. In my experience the only drug that has any value is quinidin. The method of giving quinidin is the same as in paroxysmal tachycardia.

One of the commonest mistakes encountered in the treatment of paroxysmal fibrillation is the administration of digitalis during a paroxysm. Digitalis has a tendency to prolong paroxysm rather than abolish them, so that the danger of converting a paroxysmal attack into chronic fibrillation is enhanced. If the attack tends to be prolonged, it is better to use quinidin.

In the drug treatment of chronic fibrillation the first point that has to be decided is whether digitalis or quinidin is to be employed. If the fibrillation is of recent origin and the heart muscle appears to be in relatively good condition, the use of quinidin is

justified. If these conditions are fulfilled and, in addition, the exciting cause of the fibrillation has been eradicated (after thyroidectomy, pneumonia, etc.), quinidin should unquestionably have first call in treatment. In view of the fact that fibrillation in the presence of aortic regurgitation seems to disturb cardiac efficiency more than it does in mitral disease or myocardial disease without valvular defect, I have been a little more prone to use quinidin in the aortic cases.

The details of quinidin treatment cannot be discussed here. Failure to obtain restoration of normal rhythm has been due, according to my observation, in properly selected cases principally to lack of persistence in administering quinidin or not large enough dosage. To the latter cause of failure one can have no serious objection since large doses of quinidin (3 grams daily or more) are not without danger, and should never be given unless the patient is under the closest observation. Approximately 20 per cent. of cases presumably favorable for quinidin treatment cannot be made to respond by any of the methods I have tried.

One objection to the use of quinidin and perhaps the most serious one is the tendency to recurrence of fibrillation after restoration of normal rhythm. This can be postponed indefinitely in some patients by a careful régime of life and the daily administration of small doses of quinidin, as much as 0.3 gram, three or four times a day. In other cases it is impossible to maintain normal rhythm even with large doses of quinidin. In 1 of our patients fibrillation was five times terminated by quinidin. The dosage required each time was at the rate of 4 grams daily. Each time normal rhythm was established larger dosage of quinidin was administered in the attempt to maintain it. In the last attempt 2.5 grams of quinidin sulphate was given daily in five doses, but after three weeks of this plan fibrillation again recurred. In such patients quinidin is useless.

Digitalis must remain our standby in the treatment of the great majority of auricular fibrillation. Most discussions of treatment deal with the restoration of compensation in patients with heart failure and extremely rapid ventricular rate. Much is heard pro and con concerning massive versus small divided

doses of digitalis. Except in patients on the verge of death this is a matter of little importance. In the vast majority relatively small doses will be found quite satisfactory. It is very gratifying to rescue these patients from cardiac failure, but this is really only the first skirmish. The ultimate goal should be to put them back at work and keep them there, but if this is impossible, to keep them alive and comfortable.

Digitalis is an almost perfect brake on the rate of ventricular contractions in auricular fibrillation, and it should be given solely for this braking action. The optimum ventricular rate is usually found between 65 and 90 per minute; the attempt should be made to determine as accurately as possible the best rate for each patient. Generally speaking, patients with mitral stenosis do better with the slower rate, those with aortic regurgitation with a more rapid rate.

After the optimum rate is discovered, just enough digitalis should be given to maintain the rate. It is my practice to teach my intelligent patients to count their cardiac impulse rate before arising in the morning, and, depending on whether the rate is above or below the optimum, take or omit the dosage of digitalis (usually 0.1–0.15 gram powdered digitalis) for that day. Finally, when activities are resumed, it may be necessary to increase slightly the dosage of digitalis. On such a plan it is possible for digitalis dosage to be closely gaged, and both the disagreeable effects of overdosage and the harmful effect of permitting the ventricles to beat too rapidly avoided.

Auricular Flutter.—The clinical significance and mechanism of auricular flutter are almost identical with those of auricular fibrillation, and the treatment is in most respects the same. Flutter is somewhat more responsive to quinidin than fibrillation, so that some workers regard the attempt to restore normal rhythm by the use of quinidin as the treatment of choice in dealing with established flutter. There is no serious objection to this treatment provided the ventricular myocardium is in good condition. An almost equally efficient method of restoring normal rhythm is to give large doses of digitalis which will usually convert flutter to fibrillation. If digitalis is then stopped, most

cases will revert to normal rhythm. In only 1 of our cases did chronic fibrillation result from this treatment, no effort having been made to restore normal rhythm by quinidin after the digitalis method had failed. This patient did just as well when the auricles were fibrillating as he had done when flutter was present.

Heart-block, including even minor defects in transmission, may be regarded as certain evidence of myocardial involvement, either functional or structural. Its presence, therefore, always has a special significance in respect to the management of a case. The disordered mechanism itself rarely requires treatment, although it must be remembered that minor grades of block are readily increased by digitalis. Complete or high-grade incomplete block may, however, require treatment on account of extremely slow ventricular rate or transient periods of ventricular standstill.

Transient ventricular standstill causes the well-known group of symptoms known as the Adams-Stokes syndrome. This may occur either in established complete heart-block or in cases in which complete dissociation alternates with high-grade incomplete block. In the latter type of case standstill occurs usually just after the transition to complete dissociation, the idioventricular center apparently requiring time to take up the rhythm. In this type of case, if the transitions are prevented—either by maintaining complete dissociation by digitalis or lessening the degree of block by atropin—the Adams-Stokes syndrome does not tend to occur. When the Adams-Stokes syndrome occurs in patients with established complete block the treatment is not so satisfactory. Epinephrin is of value in tiding some patients over emergency periods when attacks recur frequently. Ephedrin, because of the similarity of its action to epinephrin in accelerating the idioventricular rate, deserves a trial. I have not yet had this opportunity. A few observations published with respect to barium chlorid suggest that it may be found of value in abolishing Adams-Stokes attacks, but information at hand is too scant to afford a basis for discussion.

In some patients with complete block and myocardial weakness the slow idioventricular rate adds sufficient handicap to the circulation to produce symptoms. In such cases it would be highly

desirable to accelerate the idioventricular rate if this could be done without expense to other factors concerned in maintaining the circulation. Thyroid preparations have been found by some observers to increase the idioventricular rate, but this treatment has not attained popularity, doubtless due to the noxious effect of too much thyroid stimulation on damaged heart muscle. Epinephrin produces definite but transient acceleration of the idioventricular rate in some cases, probably those in which sympathetic innervation of the ventricular pacemaker is maintained. Because of its transient action it is scarcely a practicable remedy for continuous use, although it may be employed temporarily. The action of ephedrin appears to be similar to that of epinephrin and is longer sustained, but weaker. In one patient we obtained acceleration with epinephrin and none with ephedrin, although possibly the dosage of the latter was inadequate. Ephedrin deserves further study, as there is a possibility that it may be found useful in the treatment of this trying condition.

Another new treatment that deserves further study is the use of barium chlorid which was introduced in this connection by Cohn and Levine. Herrmann and Ashman have also been successful in raising the idioventricular rate by this method. In both groups of observations definite clinical improvement was noted. We have used barium chlorid in only 1 case, and were able by giving as much as 50 mg. four times a day to raise the idioventricular rate from 40 to 60. This patient, who was extremely decompensated, did not improve with the accelerated rate, but apparently grew worse, and finally developed pneumonia and died. We have no reason to attribute the downward clinical course and outcome to the administration of barium chlorid. It is of interest that such an extraordinary change in idioventricular rate could be produced in so ill a patient.

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THE SIGNIFICANCE OF PRECORDIAL PAIN

HEART disease, the most frequent cause of death today, is being given much thought by the medical profession and laity, as evidenced by the active wide-spread campaign for its prevention. Physicians are frequently consulted because of the presence of precordial pain. It merits the most careful consideration. The pain may arise from disease of the heart and blood-vessels, or be referred from other structures in the thorax or abdomen.

Among the commoner causes of precordial pain, organic in origin, are angina pectoris, endocarditis, myocarditis, coronary artery infarction, aortitis, pericarditis, aneurysm, intercostal neuritis, spondylitis, pleurisy, digestive disturbances, gall-bladder disease, herpes zoster, tumors and diseases involving the posterior roots of the spinal nerves, and the crisis of locomotor ataxia. Precordial pain, functional in its origin, is present in pleurodynia (intercostal neuralgia) and in the cardiac neuroses (variously termed irritable heart, soldier's heart, neurocirculatory asthenia, pseudo-angina, and effort syndrome).

Precordial pain varies in degree and in character. In the very severe cases it may be sharp, lancinating, agonizing, paroxysmal or continuous, and associated with a sense of suffocation or fear of impending death. Milder cases may manifest pain, dull aching in character, or probably only a sensation of heaviness or uneasiness. The pain may be deep or superficial. Extreme suffering is caused at times by the superficial pain produced by the pressure of the clothing on the skin.

The pain caused by organic disease of the heart, excepting pericarditis, is due to a disturbance in the nutrition of the heart

muscle. This observation is of prime importance because the presence of pain in the precordium may be the first and only symptom in the beginning of incompetency of the myocardium. As a result of the lack of nutrition the heart is unable to perform its work. The degree to which any organ of the body is capable of hypertrophying is determined by the blood-supply. When the limits of the blood-supply to the heart have been reached hypertrophy no longer can continue, and with the same or increased demands on the heart dilatation sets in, and pain to a greater or lesser degree usually accompanies it.

The heart does not possess any nerves of sensation. It is difficult to explain satisfactorily the manner in which the pain complained of in heart disease is produced. The theory advanced is that irritation of the heart resulting from pathologic changes causes impulses to pass to the spinal cord centers, where there is excited in nerve centers lying adjacent the sense of pain, which is transmitted to the structures which they control, such as muscles, areas of skin, glands, and other tissues.

The precordial pain occurring in psychic disturbances and in the cardiac neuroses is believed to originate in the cerebral centers, and is referred through the visceral segments to the cord of the precordium.

Habitual exposure to hardship and the vicissitudes of life benumbs the pain sense. Modern day living, one of luxury and refinement, as compared with that of more than several decades ago, increases the sensibility to pain.

Precordial pain of cardiovascular renal origin is usually associated with one of the following conditions:

Angina pectoris.

Acute rheumatic fever.

Infarction of the coronary vessels.

Hypertension with failure of the myocardium.

Heart failure without hypertension.

Generalized arteriosclerosis with extensive sclerosis of the cardiovascular system.

Angina pectoris, first reported in medical literature by Heberden, has been much discussed, not well understood, and

a much feared diseased condition. By some authorities it is believed to be a distinct clinical entity, and by others a syndrome. The latter view is probably correct. Many explanations of angina pectoris have been offered. The two most widely accepted views of today are: first, that it is a disease primarily of the coronary arteries, that is, thrombosis, infarction, or spasm; second, that the lesion is in the first part of the aorta, thereby obstructing the orifices of the coronary arteries.

Necropsy upon patients who have died of angina pectoris frequently discloses healed and, less commonly, recent infarction in the coronary vessels. Patients also come to autopsy showing similar lesions, without having presented at any time symptoms of angina pectoris. It would, therefore, appear that there is no constant pathology in the coronary arteries in angina pectoris.

At present it is reasonably certain that angina pectoris is the result of an inflammatory lesion in the beginning of the aorta which results in interference with the proper blood-supply to the heart muscle, with the possibility that the inflammatory process obstructs the mouth of the coronary vessels. This obstruction at times causes thrombosis and infarction, which may be accompanied by pain, but of a different character than that of angina pectoris. The pain of the angina pectoris is believed to be due to the stretching of the outer coat of the first part of the aorta (which is rich in nerve supply) caused by increased peripheral vascular resistance in response to increased body effort. The nervous impulses generated in the wall of the aorta are transmitted to the cardiac plexus by the fibers surrounding the external coat of the aorta. The initial seat of the pain is in the region corresponding to the plexus, *i. e.*, the retrosternal portion of the precordium.

The nerve impulses originating in the filaments surrounding the external coat of the aorta having been transmitted to the cardiac plexus, then are conducted by the sympathetic system and pressor fibers of the vagus nerve. The sympathetic fibers carry the sensations by way of the cervical sympathetic ganglia to the spinal cord by means of the posterior roots of the eighth cervical and the first and second thoracic nerves. The painful

sensations are distributed toward the periphery by these nerves which give off the circumflex, the internal cutaneous, and the ulnar nerves.

The pain of angina pectoris usually occurs in the retrosternal portion of the precordium in the region of the second and third left interspaces. The pain occurs in paroxysms and is usually referred to the left shoulder and left forearm, or to both forearms. It may be referred into the neck and even be felt in the lobes of the ears. The pain occasionally instead of being referred down the arm, may be felt in the finger-tips and travel up the arm, or the pain may be experienced as extending up or down the arm with a sensation of being a tight band around the wrist. The paroxysms of pain of angina pectoris seldom lasts more than five minutes, usually less, but may be repeated at frequent intervals. They may be initiated by the slightest effort, mental or physical. Emotional disturbances, grief, anger, the taking of food, hearty laughing, walking against the wind, ascending stairs, are capable of provoking an attack. At times the slightest effort may bring on an attack, and, again, the patient is capable of greater exertion without inducing an attack.

Although attacks do not occur as frequently when at mental and physical rest, the patient may awake from his sleep because of a paroxysm.

Accompanying this pain, which is referred to as agonizing or terrifying, is the sensation as if the heart is being grasped and held tightly by a strong, gripping hand. The patient is practically motionless during an attack, a most important point in differentiating this pain from other conditions resembling it. The facies during an attack denote the anguish which the patient suffers. Associated with these painful sensations is the sense of impending death, which is the patient's mental reaction to the severe pain.

The attacks of angina pectoris occur more frequently in men than in women, and seldom before the age of forty years. Literature records the case of true angina pectoris in a boy eighteen years of age, in which the diagnosis was verified at the autopsy.

The etiology of angina pectoris is obscure, but all conditions which favor the development of arteriosclerosis may be looked upon as predisposing causes.

The physical examination of the heart and the electrocardiograms of patients suffering from angina pectoris may be normal. The pulse during the attack may be normal in rate, at times it is slowed, but seldom accelerated. It is usually full and strong. If the angina is accompanied by extensive cardiovascular renal disease, the blood-pressure is likely to be high; otherwise it is normal. It is also well to remember that attacks of angina pectoris may cease when heart failure sets in. Digitalis given to patients during the intervals of attacks of angina in the absence of heart failure may cause the attacks to occur more frequently. The pain of gall-bladder disease and the attacks of angina are present in the same individual at times, and may be mistaken one for the other.

Occlusion of the coronary artery by embolism or by thrombosis may be accompanied by precordial pain. In most instances the sudden blocking of the larger coronary arteries is followed by immediate death, but occlusion of the smaller coronary branches is not necessarily fatal. When the pain is precordial it is usually severe, and is described as choking, oppressive, or suffocating. If a larger branch of the coronary vessel is occluded, the pain, accompanied by shock and its attending phenomena, such as increased pulse rate, cold, clammy skin, restlessness, dyspnea, and pulmonary edema, is continuous, and usually lasts over a greater period of time than an attack of angina pectoris. The blood-pressure usually falls during a severe attack of infarction of the coronary vessel.

The pain is less likely to be referred to the neck and down the left arm than in angina. Nitrites give little if any relief, and ordinary doses of morphin are of little avail; $\frac{1}{2}$ grain of morphin, repeated, is necessary to give relief from the pain. If the patient survives for twenty-four hours, fever and leukocytosis usually develop, and a pericardial friction sound is often heard overlying the course of the vessel affected.

Accompanying an attack of occlusion of the coronary vessel

the pulse at times becomes irregular, usually due to auricular fibrillation, less frequently because of extrasystoles.

Cardiac failure may develop if the patient survives a severe attack lasting for a period of a week or more, as illustrated by a patient recently observed. A woman, sixty-six years of age (previously subjected to mild attacks of angina) was seized with intense precordial pain which was not relieved by a nitroglycerin tablet. The pain was low, substernal, and accompanied by restlessness, anxiety, increased pulse rate, and some cyanosis. Gas pains were thought to be the cause of the trouble. Bicarbonate of soda and, finally, induced vomiting failed to relieve the suffering. A physician was called, who administered $\frac{1}{4}$ gr. of morphin sulphate, and three $\frac{1}{4}$-gr. tablets, given hypodermically, were necessary during the course of the next two hours to quiet the patient. Although the administration of morphin sulphate gave relief, the patient constantly pointed to a small area of pain in the lower right portion of the precordium which was extremely painful to the touch.

The systolic blood-pressure, which previous to the attack averaged 160 mm. Hg., dropped to 130 mm. Hg. within twelve hours after the onset of the attack.

On the following day a pericardial friction sound was heard in this region; fever and leukocytosis were present. Three days later a loud, systolic murmur was heard over the body of the heart. The area of cardiac dulness was increased to the left, the liver was palpable, and edema of extremities was present. Heart failure gradually developed, lasting three weeks from the beginning of the attack until death occurred, and closed the clinical picture of infarction of the coronary vessels.

In this case pulmonary edema was not present early in the attack, but congestion of the lungs developed four or five days after the beginning of the attack. Although no autopsy was obtained, the three physicians who observed the patient believed it to be an instance of coronary occlusion occurring in a victim of angina, eventuating in acute failure, followed by death.

Precordial pain occurs in individuals who are of a neurotic temperament. It was present to a large extent among the

soldiers of the recent war, who suffered from neurocirculatory asthenia. This type of precordial pain and associated symptoms was first described during the Civil War by J. M. DaCosta as the "soldier's heart." This syndrome is also known under various names, such as nervous heart, cardiac neurosis and pseudo-angina, and occurs in individuals of a neurotic temperament in civil life. The attacks are precipitated by multitudinous worries and anxieties to which these individuals subject themselves. This type of patient is very likely to be a heavy user of tobacco, tea, or coffee. These excesses favor the occurrence of the attacks. The patient, as a rule, complains more of the oppression than of the severity of the pain, and is very apprehensive. During the attack the patient is restless, if not hysteric, and may complain of vertigo and syncopal attacks.

The pains may be continuous from day to day until the worries or anxieties are removed.

There should be no difficulty in differentiating a functional precordial pain from true angina and those due to obliteration of branches of the coronary vessels. The attacks of pseudo-angina occur in the young of a neurotic temperament who over-indulge in tea, coffee, and tobacco, and usually other nervous phenomena are present. Mottling of the skin, especially of the forearms, often is present in this type of patient. The cause of this pain, if nervous, is central in origin. If toxic in origin, caused by the excessive use of tobacco, coffee, and tea, it may be due to spasm of the coronary vessels.

Probably the most common cause of precordial pain is cardio-vascular renal disease associated with constant hypertension. The exact cause of the precordial pain is not satisfactorily explained. The theories that anemia and spasm of the coronary vessels are the cause have not been proved. It is more likely that it is either toxic or due to a lack of proper blood-supply to the myocardium. These changes, when present, are usually found in patients more than fifty years of age whose hearts show hypertrophy. The mitral and the aortic valve leaflets are thickened with some aortitis and thickening of the coronary vessels. These changes may also be present in an individual without any pre-

cordial pain. In a smaller group of patients the precordial pain may be associated with a wide variation in blood-pressure. A patient may have the previously described symptoms, except that when his blood-pressure is 160 mm. Hg. no precordial pain is present. Slight excitement or physical effort may cause a rise in his blood-pressure of 30 to 40 mm. Hg. and precordial pain occurs. The return of the blood-pressure to 160 mm. Hg. results in the disappearance of the pain.

Associated with the symptoms of chronic uremia, such as headaches, nausea, vomiting, varying degrees of anemia, mental disturbances, fleeting palsies, attacks of paroxysmal dyspnea, hypertension with high diastolic reading, attacks of precordial pain occur which are not relieved by nitroglycerin or digitalis. These pains are apparently toxic in origin, affecting the nutrition of the heart muscle.

The very first symptom of which a patient may complain when the myocardium begins to fail and before the patient has had reason to believe that his heart was not doing its work is precordial pain without hypertension. The complaint is most common in patients between the ages of fifty and sixty years, who have a blood-pressure of 150 to 160 mm. Hg. with negative urinary findings. The patient notices that physical effort, which before had caused no inconvenience, now produces some precordial pain. The pulse is regular, but moderately increased in rate, 85 to 95 per minute.

Digitalis, with restriction of physical effort, usually benefits the patient with this type of precordial pain. Caution as to his activity thereafter is of assistance in keeping the patient free from this pain.

Focal infections should always have attention in preventing the progress of myocardial disease.

Patients who suffer from rheumatic manifestations frequently complain of precordial pain, associated with mitral valve disease, usually the stenotic form. The pain is described as sticking. Slight elevation in temperature may be present. The cause of these pains which usually are associated with an increase in pulse rate, joint pains, however slight, appear to be exacerba-

tions of a rheumatic endocarditis. Careful attention to this precordial pain by prompt rest in bed and full doses of salicylates may avert a more severe attack of rheumatic fever. The pain of mitral stenosis may be difficult to relieve during the quiescent period.

Aortitis is another common cause of precordial pain. It is either syphilitic or rheumatic in origin. The pain is dull and substernal in character and is due to inflammation and subsequent dilatation of the aorta. The root of the aorta is surrounded by a rich nerve-supply and pain is very evident, especially when effort is made, thereby increasing intra-aortic tension and stretching its walls. The precordial pain complained of in cases of aortic regurgitation is due to the accompanying aortitis.

Occasionally in the young the presence of precordial pain is associated with generalized arteriosclerosis. This pain may be present for months before other symptoms develop, with hypertrophy of the heart, a low urine specific gravity, eye-ground changes, hypertension, and dyspnea on slight effort.

The pain caused by aneurysm of the arch of the aorta may be precordial in its location and is due to pressure on the surrounding structures and intercostal nerves. Roentgen-ray examination and the presence of expansile pulsation with other pressure phenomena will be of assistance in the recognition of this condition.

The precordial pain due to pericarditis is usually associated with fever and an inconstant to-and-fro friction sound synchronous with the heart-beat. The pain may be stitch-like and lancinating or dull and heavy; it is seldom referred beyond the borders of the heart, although at times it may be referred to the left shoulder, the left arm, or the epigastrium. Frequently it is located at the base of the heart where the pericardium is reflected on to the great vessels. Its rather frequent occurrence in advanced nephritis must be kept in mind.

Patients with definite gastric disturbances, especially in which epigastric distress is present, may suffer from pain referred to precordium. The gastric symptoms are not unlike those of gastric ulcer, pain in the epigastrium, hyperacidity,

gaseous distention, belching, and the referred pain to the precordium, which is *neuralgic, fleeting*, and *inconstant* in character, and disappears with an antacid medication and diet regulation.

Women at the menopause may complain of more or less precordial pain which does not yield readily to treatment. This pain occurs without any evidence of disease of the cardiovascular renal system. It may, however, be a forerunner of early myocardial insufficiency, but it is more commonly the result of vasomotor disturbances of the heart.

Precordial pain without any signs of decompensation of the heart may occur in association with severe bronchitis and pneumonia. This condition clears up promptly without any deleterious effect. It merits consideration because precordial pain accompanies infections of the lungs in which symptoms of myocardial failure do occur, and while the former requires no special treatment, the latter requires rest in bed until the acute manifestations of heart failure disappear.

Some patients, mostly of middle age, complain of a dull, aching pain over the precordium more or less constant in character, bearing little relation to rest or activity. Careful search for the cause shows nothing abnormal but oral sepsis or diseased tonsils. The proper treatment of the foci of infection causes the pain to disappear. Nine months ago an Italian male patient, forty-two years of age, who worked in a repair gang on the railroad, applied to the Jefferson Hospital for treatment, stating that he had been unable to work for six months because of severe precordial pain, which progressively became worse since an attack of grippe in 1920. Careful study and observation revealed nothing to account for his pain except badly diseased tonsils. The tonsils were removed, and the patient was free from pain at his visit about one month ago.

Dropped beats, or premature contractions, or extrasystoles, all referring to the same condition, are capable of causing a precordial pain or distress. The condition is recognized by the occurrence of an irregular pulse, which tends to become aggravated while at rest. The irregularity usually disappears with effort and exercise. In doubtful cases it may be necessary to use the

electrocardiograph to recognize the nature of the irregularity causing the distress or pain.

Functional and organic disease of the esophagus may be the cause of referred pain to the precordium. Carcinoma, syphilis, ulceration, diverticula, and spasm (functional in character) of the esophagus are the usual causes.

The pain of intercostal neuritis may be most intense over the precordium, but its recognition is easy if tenderness is noted along the course of the nerve. Spinal caries, tumors of the spinal cord, spondylitis causing intercostal neuritis may cause constant intense pain in the precordial area. Herpes zoster may be the cause of precordial pain and a dull ache may persist following the complete healing of herpes. Pleurisy in the region of the heart will cause precordial pain which is recognized by auscultation disclosing a friction sound corresponding in rate to the number of the respirations.

The precordial pain resulting from intercostal neuralgia is also limited to the nerve trunks and is paroxysmal. There are tender points along the course of the nerve. It is a chronic condition and occurs in neurotic and hysteric individuals.

In conclusion, the study of precordial pain reveals many possibilities as to its cause, but the satisfaction that comes to the physician in being able to recognize that cause and, if possible, relieve the pain is most gratifying.

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DIFFERENTIAL DIAGNOSIS OF HEMORRHAGIC CONDITIONS: AN OUTLINE

PATHOLOGIC hemorrhage of any kind, be it internal or external, has two possible causes—a local cause and a systemic cause. We would designate as local causes all pathologic processes which operate in the production of local hemorrhage by purely local invasion, from without, of contiguous blood-vascular tissue. These local causes comprise the local effects of local (1) inflammation, (2) ulceration, (3) neoplasm, and (4) trauma. Systemic causes, on the other hand, are those which produce either local or generalized hemorrhages by reason of intrinsic disease of the blood and blood-vascular tissue itself.

I propose to discuss the various types of hemorrhage of the latter group, and shall present (1) a list of hemorrhagic symptoms, (2) a working classification of the systemic diseases which may produce these symptoms, (3) an epitome of the known mechanisms whereby these symptoms are produced, (4) an outline of various procedures that are helpful in differential diagnosis, and (5) some personal observations concerning the value and limitations of these diagnostic procedures.

The point of view of this discussion is intended to be a broad one—perhaps unconventional, but none the less useful, I think—which encompasses such divergent conditions as cerebral hemorrhage due to nephritis, arteriosclerosis, and hypertension, on the one hand, and melena neonatorum and hemophilia on the other, but which excludes perforce such conditions as melena due to peptic ulcer and cerebral hemorrhage due to fracture of the skull. For the sake of convenience we may adopt the old

phrase "hemorrhagic diathesis" as a generic designation, including the various types of hemorrhage of systemic blood and blood-vascular origin with which we are now concerned.

According to our usage, hemorrhagic diathesis may be defined as a symptom-complex characterized by an abnormal tendency to bleed from the body surfaces or into the body tissues without adequate local cause or out of all proportion to local cause. It follows from this definition that our subject includes, in addition to hemorrhage of purely systemic origin, also hemorrhage initiated by local cause, but sustained and exaggerated by pre-existing systemic conditions. Furthermore, it must not be forgotten that our subject includes certain generalized hemorrhagic states immediately based on systemic disease of the blood and blood-vessels, even though such systemic disease may have been itself induced by the long-continued effect of local cause. Thus here, as in every other field of investigation, when we dig back of immediate and "liberating" causes to more fundamental ones, our artificial divisions and classifications merge into one another.

It is utterly impossible in a discussion of this kind even to mention the innumerable local causes of local hemorrhage. These local causes have to be excluded before one has a right to consider any local hemorrhage as a manifestation of hemorrhagic diathesis. We must assume that such local causes of local hemorrhage have been excluded in every instance which we shall discuss, lest our outline swell to text-book proportion.

The practical usefulness and importance of our division of hemorrhagic phenomena into two classes will, I think, become apparent to you as we proceed. For example, consider the symptom "bleeding gums." A patient with this complaint will probably go first to his dentist. Assuming that this patient is not one of the much advertised "four out of five" pyorrhea victims, and that his dentist finding no adequate local cause, wisely refers the patient to you, what are the etiologic possibilities? Again, your colleague—the gynecologist—may send you a patient with this history: Miss X has menorrhagia, and there is nothing to be found in the pelvic organs to account for it. What

systemic conditions must you consider and what procedures must you undertake to make the proper diagnosis in this case?

Medical practice in almost any branch frequently presents this self-same dual problem: Is such and such symptom or group of symptoms due to purely local cause or to some systemic cause? I invite you to view the symptom, hemorrhage, from the same standpoint, and hope to give you a helpful glimpse of one-half of the picture.

The clinical manifestations of a hemorrhagic diathesis may include one or more of the following, which are listed approximately in order of frequency of occurrence: bleeding gums, epistaxis, purpura and ecchymosis and abnormal bleeding from local injury, melena, menorrhagia and metrorrhagia, hematuria, retinal hemorrhage, cerebral hemorrhage, subconjunctival hemorrhage, hematemesis, hemoptysis, omphalorrhagia, hemarthrosis, hematomyelia, hemathorax, hematopericardium, hematocelia. The only other clinical symptoms commonly found in association with the various forms of hemorrhagic diathesis are slight fever and anemia, but neither of these is a necessary concomitant.

Obviously, as we have mentioned above, no one of these hemorrhagic phenomena is in itself pathognomonic of a hemorrhagic diathesis. Indeed, it is a safe rule of practice to view all local hemorrhage as due to local cause until proved otherwise, but local hemorrhage is often the first manifestation of a systemic hemorrhagic condition and sometimes the only external manifestation thereof. Furthermore, multiple or generalized hemorrhages and purpura are almost invariably the result of hemorrhagic diathesis. We are concerned with this side of the picture only and with the many systemic diseases exhibiting a hemorrhagic diathesis. These diseases may be conveniently grouped as follows:

(1) Hemorrhagic diathesis due primarily to disease of blood and blood-forming organs: 1, Purpura hæmorrhagica (idiopathic); 2, hemorrhagic disease of the newborn; 3, aplastic anemia; 4, pernicious anemia; 5, hemolytic ictero-anemia, splenic anemia, and Banti's disease; 6, the leukemias, including

aleukemic leukemia; 7, polycythemia vera; 8, Hodgkin's disease; 9, Gaucher's disease.

(2) Secondary hemorrhagic conditions in: 1, Anemia of chronic loss of blood (*e. g.*, hemorrhoids, peptic ulcer, fibroma uteri); 2, anemias and vascular disturbances due to exogenous toxins (*e. g.*, benzol and arsphenamin poisoning); 3, anemias and vascular disturbances due to endogenous toxins, metabolic and endocrine disorders (*e. g.*, scurvy, myxedema, anemia of pregnancy, chronic nephritis, hypertension and arteriosclerosis, paroxysmal hemoglobinuria, obstructive jaundice, and degenerative disease of the liver); 4, blood-vascular disturbances due to infection (*e. g.*, septicemia, subacute infective endocarditis, "focal infection" state, hemorrhagic forms of acute exanthemata, generalized tuberculosis, syphilis); 5, cachexia of malignancy; 6, anaphylactic shock.

(3) Hemorrhagic diathesis due to hereditary and other unknown factors: 1, Hemophilia; 2, hereditary hematuria[1]; 3, hereditary hemoptysis[2]; 4, hereditary hemorrhagic telangiectasia[3]; 5, hereditary thrombasthenia.[4]

It will be seen at a glance that the above is merely a convenient grouping and by no means a scientific classification—which would require a more complete knowledge of pathogenesis than we possess at the present time. Furthermore, some of the subdivisions are not mutually exclusive. The common denominator in all, however, is the occasional or frequent occurrence of abnormal bleeding. In some the hemorrhagic diathesis is the outstanding feature—as in hemophilia, purpura hæmorrhagica, and melena neonatorum. In others it is a not uncommon manifestation, as in chronic hypertensive cardiovascular-renal disease, aplastic anemia, and bacterial endocarditis. In a third group it is a rare concomitant, as in Hodgkin's disease, polycythemia vera, and pernicious anemia.

Some of the diseases are so dissimilar and unrelated—except when a hemorrhagic aspect supervenes—that one can hardly imagine the necessity of having to think of them all in assaying a given hemorrhagic symptom. Yet it is important at least to mention them all. I have been told of one recent instance in

which a patient with hemorrhagic smallpox was treated for some time in a general medical ward for supposed "toxic purpura." I know a gentleman with polycythemia vera who consulted several ophthalmologists because his eyes were bloodshot and painful, without securing either relief or a correct diagnosis. This same patient had bleeding gums which several dentists attempted to cure by local measures. Four months ago a young woman, who had been curetted three times without relief within a period of several years for supposed "myopathic uterine hemorrhage," was found to have chronic purpura hæmorrhagica. A splenectomy has cured her of all symptoms to date.

These examples could be multiplied indefinitely, but will suffice to emphasize the point that by merely thinking of the possibilities when confronted by hemorrhagic phenomena a long step is made toward arriving at the diagnosis. It is obviously impossible to discuss the history, physical signs and symptoms, and the general differential diagnosis of diseases capable of producing hemorrhagic diathesis. The differential diagnosis of retinal hemorrhage alone would fill a large volume. I shall have to be content merely to remind you of possibilities.

The various forms of hemorrhagic diathesis have no uniform fundamental mechanism that is known at the present time. Indeed, it is certain that a different mechanism is operative in different conditions. The occurrence of abnormal bleeding must, on *a priori* grounds, be based on one or more of the following factors: (1) Abnormal permeability of the capillaries, or failure of normal closure of ruptured capillaries; (2) abnormal penetrating qualities of the blood; (3) defective clotting power of the blood and tissue juices. Various methods have been devised to demonstrate the presence or absence of these several factors in clinical practice.

The demonstration of abnormal capillary permeability is not difficult. This defect is found in all forms of hemorrhagic diathesis, and is especially marked in the purpuras, in arteriosclerosis, and in certain acute intoxications and infections of systemic nature (*e. g.*, subacute infective endocarditis).

The failure of normal closure of ruptured capillaries is assumed to occur in conditions of generalized vascular sclerosis and also in hereditary hemorrhagic telangiectasia,[3] with its congeries of unprotected capillaries lacking in contractile power. The effect of high blood-pressure in keeping open a ruptured vessel or in determining the rupture of a diseased vessel is obvious.

Abnormal penetrating qualities of the blood cannot be proved. It seems probable, however, that in states of anemia in which the blood viscosity is known to be greatly reduced this factor might be of considerable importance in favoring seepage of blood.

Defective clotting power of the blood is readily demonstrable in certain hemorrhagic conditions which we shall discuss later.

Differential diagnosis of diseases associated with hemorrhagic diathesis requires a special approach and a special technic of its own, and, in addition, demands at times a painstaking survey involving almost every diagnostic method known to medical science. The details of technic may be found in textbooks and laboratory manuals; the following outline will serve as a helpful reminder of the procedures that may be employed in arriving at a correct diagnosis of hemorrhagic conditions:

(1) The ordinary complete blood-count is the first step in any hematologic study. The diagnosis of the leukemias, various anemias, and polycythemia is often made by this simple procedure alone. In addition, the experienced hematologist is usually able to form accurate conclusions regarding the state of the hemopoietic organs and the blood-platelet content by inspection of properly stained smears. Wright's stain is the best for routine purposes. An oxydase stain is sometimes helpful in the differentiation of the acute leukemias. Cresyl blue stain is employed to estimate bone-marrow activity as evidenced by reticulosis of the erythrocytes.

(2) Platelet counts should be made in every instance of suspected hemorrhagic diathesis. This procedure requires care, speed, and experience for trustworthy results. The repeated finding of thrombocytopenia in any given case is diagnostic of

purpura hæmorrhagica. This disease occurs in two chief forms—first, the primary or idiopathic type, formerly called Werlhof's disease; and second, the symptomatic type of purpura hæmorrhagica. This secondary type has been observed in certain forms of tuberculosis, hemorrhagic smallpox,[5] septicemia, lymphatic leukemia, the last stages of aplastic and myelophthisic anemia, in certain types of Banti's disease,[6] and experimentally in anaphylactic shock.[7] The only fundamental difference between these secondary forms of purpura hæmorrhagica and the primary form of the disease lies in the knowledge of a cause in the first group and a total absence of such knowledge in the latter. The hemorrhagic diathesis is identical in all, and its characteristic is a thrombocytopenia, at least during the active phases. This characteristic differentiates purpura hæmorrhagica, both primary and secondary, from the other forms of purpura and from hemophilia, and, indeed, from all the other types of hemorrhagic diathesis. A subnormal platelet count is usually associated with a prolonged bleeding time and a subnormal clot retraction—all three of which are found in purpura hæmorrhagica. In contrast to this, hemophilia presents a normal platelet count, a normal bleeding time, and a normal clot retraction, but a delayed clotting time.

It is supposed that the quantitative deficiency of platelets accounts for the hemorrhagic phenomena of purpura hæmorrhagica, while a qualitative defect of platelets is postulated in hemophilia.[8] A somewhat different view, however, has been advanced by Glanzmann[4] in his work on the condition which he terms "hereditary hemorrhagic thrombasthenia," to which further reference will be made.

The rôle of the reticulo-endothelial system and especially of the spleen in the pathogenesis of thrombocytopenia now occupies the foreground of hematologic investigation.[9]

Before leaving the subject of platelet counting it should be stated that variations in size, shape, and staining characteristics of platelets are thought by some hematologists to be of diagnostic significance. Personally, I do not feel that deductions from such variations are justifiable at present.

(3) Clotting time tests should be performed with venous blood only, obtained by accurate venipuncture and received without undue agitation in clean tubes washed in normal salt solution. The various methods of clotting time determination based on the use of capillary blood obtained by finger prick are all inaccurate because of the inevitable admixture of tissue juices. In some cases of hemophilia the blood obtained by finger prick clots normally, and thus a serious diagnostic error may be made. Prolonged clotting time occurs to a most marked degree in hemophilia; to a less exent in chronic obstructive jaundice and in experimental anaphylactic shock. In the other forms of hemorrhagic diathesis the clotting time is practically normal.

(4) The bleeding time test (Duke) is of confirmatory value in the diagnosis of purpura hæmorrhagica, during active phases of which a prolongation of bleeding time is usually found.

(5) Clot retraction test, when properly performed, also parallels in a rough way the platelet count, but with less clear-cut and less significant results.

According to Glanzmann[4] an hereditary background is demonstrable in many cases of purpura hæmorrhagica (idiopathic). He cites a number of bleeder families in which several of the members, both male and female, presented typical thrombocytopenic purpura, while other members with more or less active hemorrhagic manifestations had normal platelet counts. All, however, presented evidences of abnormal clot retractility. He was able to demonstrate with isolated blood-platelets from these individuals two characteristics: (*a*) abnormal fragility of platelets, and (*b*) lack of the normal element responsible for clot retraction. He gives the name "hereditary hemorrhagic thrombasthenia" to this group, which he believes to be the hereditary constitutional background and progenitor of idiopathic purpura hæmorrhagica.

Glanzmann postulates, as a logical result of his experiments, the existence in blood-platelets of a "thrombozym" essential to thrombin formation, and a "retraktozym" responsible for clot retraction. The platelets in hereditary hemorrhagic thrombasthenia and purpura hæmorrhagica, he finds, are not only ab-

normally fragile but also are deficient in "retraktozym," though possessing their normal quantum of "thrombozym," which is readily available on account of their increased fragility. In contrast to this, hemophilic platelets are abnormal only in their diminished fragility (*i. e.*, their excessive resistance to lysis), which would explain not only the delay of clot formation in hemophilia but also the normal clot retraction when once the clot is formed.

According to modern ideas, hemophilia is not exhibited by females, though they are "conductors" of the disease. Glanzmann's work certainly strengthens this modern view, as it offers a ready explanation for some of the otherwise unclassified cases of hereditary hemorrhagic diathesis in the female.

Clot retraction tests as ordinarily performed are not productive of uniformly reliable results. Dr. Appel and I are carrying on work at the present time which we hope will help to standardize this procedure.

(6) The capillary resistance test, or tourniquet test, gives results which are merely of suggestive value. In most cases of hemorrhagic diathesis a positive test may be obtained, but the same result is also obtained in many normal children and in some adults without hemorrhagic disease.

It is interesting that this test was first proposed by Rumple[10] as a pathognomonic sign of early scarlet fever. Subsequently Leede[10] showed that a positive tourniquet test, while occurring in most cases of scarlet fever, could also be obtained in other conditions. Hecht[11] and, later, Michael[12] demonstrated the non-specific character of the results, and we have reached the same conclusion here. In this connection the report of Arnett and Weidmann is interesting.[13]

Anyone who has performed this simple test will have noted the variability of results obtained by varying degrees of constricting pressure.[14] I think the best procedure is that originally advised by Leede, namely, the use of a blood-pressure instrument cuff at 60 mm. for ten minutes.

(7) The fragility of the erythrocytes, as tested by graded strength hypotonic salt solutions, is of value in the diagnosis of hemolytic diseases, especially of hemolytic ictero-anemia.

(8) Tests for urobilinuria and excess urobilin in the stools are also helpful in diagnosis of excess hemolysis.

(9) The van den Bergh test for bilirubinemia is a recent valuable asset to the student of hemorrhagic diseases. By means of this test the differentiation between hemorrhagic aspects of hemolytic and obstructive jaundice can be made with accuracy. Furthermore, some insight into the functional state of the liver cells can often be gained, and thus one of the possible systemic causes of hemorrhagic diathesis (*i. e.*, liver degeneration) may be discovered. Another interesting possibility inherent in this test is the diagnosis of concealed hemorrhage. This test should be employed more widely than it has been in the study of hemorrhagic diseases.

(10) The usual blood chemistry studies of clinical practice, aside from establishing or disproving the existence of severe nephritis with its occasional hemorrhagic aspects, are of little or no practical help to us in this special subject. Blood calcium estimations in hemorrhagic states are within normal limits even in obstructive jaundice. Blood fibrinogen is reduced in severe hepatic degeneration, but is practically normal in other hemorrhagic conditions. Estimations of prothrombin time parallel the clotting time and are superfluous. Accurate estimations of "antithrombin" are too complicated for clinical use.

(11) Blood Wassermann tests should be "routine." A true hemorrhagic diathesis due to syphilis is unknown except in hemorrhagic disease of the newborn, where it plays a definite rôle, and in such conditions as retinal hemorrhage, cerebral hemorrhage, hematomyelia, and other local evidences of generalized blood vascular degeneration. Hemorrhagic diathesis due to antisyphilitic treatment (arsphenamin especially) should not be forgotten. You will be cautioned by some authors that a "false positive" Wassermann test is not uncommon in any serious blood dyscrasia,[15] but we have not found this to be the case.

(12) Tests for occult blood in stool, urine, and gastric juice, together with examinations of stools for ova of parasites, and testing for the presence or absence of hydrochloric acid in the gastric juice, complete the list of technical procedures especially

adapted to the needs of the student of hemorrhagic diathesis. The relation of these procedures is obvious.

x-Ray studies of various types are of tremendous value in disclosing the presence or absence of local causes for hemorrhagic manifestations. There are but few instances, however (*e. g.*, scurvy), in which the roentgenologist is able to make a positive diagnosis of a true hemorrhagic disease.

Miscellaneous procedures, such as blood-cultures, chemical and bacteriologic examination of secretions, basal metabolism determinations, and even biopsy study of superficial glands may all prove helpful in the exceptional case. Capillariscopy by Lombard's method is easy, but of little practical clinical value. The help of the various specialists in their respective fields is important in excluding local causes as well as in making a complete diagnosis. Especially valuable are the results of ophthalmoscopy, cystoscopy, proctoscopy, and neurologic examinations.

Finally, but of prime importance, a careful and detailed history both personal and familial and a minute and complete physical examination must precede—as a *sine qua non*—all that has gone before in this outline.

Summary.—An attempt is made to present a broad view of hemorrhagic phenomena arising from systemic disease of the blood and blood-vascular tissues. The presentation includes an enumeration of the hemorrhagic phenomena themselves, a clinical classification of underlying systemic diseases responsible for them, an epitome of the known mechanisms and theoretic explanations of their production, and an outline of technical procedures helpful in arriving at a proper diagnosis.

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THE DIFFERENTIAL DIAGNOSIS OF CONGENITAL HEART DISEASE

THE picture of congenital heart disease in the mind of the average physician is that of a "blue baby," doomed to early death, or of a young individual stunted in growth, presenting marked cyanosis, clubbed fingers, bizarre heart findings, the prey of infections, and subject to suffocating attacks that may quickly terminate life. In other words, the general conception is that of congenital cyanosis with its familiar symptom-complex and gloomy prognosis. Feeling that these cases are relatively few, that they are difficult of analysis, and that there is nothing to be done, scant attention is paid to them.

If this were the whole story of congenital heart disease, such a pessimistic attitude would be justified. But I propose today to call your attention to a larger and more important group of individuals with congenital heart disease, who present no evidences of cyanosis, who have slight or no cardiac symptoms, and who may live out in perfectly healthy fashion a normal span of years if they are given that preventive care so freely accorded other "potential cardiacs." It has been my good fortune during the past two years to have had the opportunity of studying the clinical and morphologic features of congenital heart disease with Dr. M. E. Abbott, who in a monograph on this subject, in Osler and McCrae's System of Medicine, and in her other writings[1] has done much to clarify our knowledge of this important subject. The following remarks present a brief summary of our studies, and I take this opportunity to express my indebtedness to Dr. Abbott for placing her material so generously at my disposal.

To state anatomically what I have just said about the two groups of congenital cardiac disease, we must understand that congenital defects introduce a mechanical interference in the normal course of the circulation which may lead to undue strain upon certain parts of the heart or may permit of abnormal communications between the venous and arterial sides of the heart, by means of which the oxygenation of arterial blood may be lessened. Such abnormal communications may be simple, localized apertures between the right and left sides of the heart or between the pulmonary artery or the aorta; or they may be such gross defects as to lead to actual deflection of the blood channel, so that most of the volume of venous blood arriving at the heart may be injected into the arterial stream. Under the former circumstances the blood flow through the abnormal opening takes place from the chamber in which the pressure is higher into the side in which the pressure is lower. Therefore, we have two groups of congenital cardiac lesions presenting a very different clinical picture, according as venous blood passes into the arterial, or arterial blood into the venous—the former presenting the true symptom-complex of congenital cyanosis, and the latter an equally distinctive syndrome with complete absence of cyanosis except as a transient or terminal feature. We are indebted to Abbott for the descriptive terms, "venous-arterial" and "arterial-venous shunt," applied to these anomalies of the circulation.

Let us consider first the venous-arterial shunt or the cyanotic group of congenital cardiac disease. No attempt will be made to include all the varieties of congenital defects of either group. The discussion will be limited to the most frequent and most important lesions.

CYANOTIC GROUP (VENOUS-ARTERIAL SHUNT)

Such a disturbance of the circulation may occur in several ways: (1) By direct right-to-left shunt through a ventricular septal defect, when the pressure is higher in the right ventricle, as is the case in the instance of an associated pulmonary stenosis; (2) by direct admixture within the chamber which may occur because of complete absence of the cardiac or arterial septum;

(3) in dextroposition of the aorta, when the mouth of the aorta overrides the right ventricle, venous blood passing directly from the right ventricle into the systemic aorta. Under such circumstances the conditions are present for the development of a true congenital cyanosis, and it is of the commonest member of this group that I wish to speak. The anomaly referred to is a form of pulmonary stenosis, which is probably the commonest of all cardiac defects and the type most familiar to the practitioner. In the lesion about to be described pulmonary stenosis is associated with a defect of the ventricular septum at the base and overriding (dextroposition of the aorta). It has been termed by the French "the tetralogy of Fallot," in which hypertrophy of the right ventricle makes up the fourth anatomic finding of the anomaly. The following case is illustrative of the anomaly under discussion:

A. B., a white male, aged twenty-two years, was admitted to the Tuberculosis Ward of the Philadelphia General Hospital, on the service of Dr. S. A. Loewenberg, August 4, 1922. He complained of cough and blood-spitting.

The family history was negative. The patient had never been in good health. He was always more or less cyanosed, and had a long history of gastro-intestinal disturbance. He caught cold early in the winter of 1922, and had a cough and expectoration since. There had been considerable loss of weight. A week prior to admission he had a frank pulmonary hemorrhage, and since then, blood-spitting. On admission to the hospital the patient was markedly cyanotic, and the fingers and toes clubbed. Examination of the chest revealed evidences of pulmonary tuberculosis. The heart seemed enlarged both to the right and left, the apex-beat was forceful in the sixth interspace to the left of the nipple line. There was a systolic thrill over the base of the heart and in the third interspace to the left of the sternum, and a harsh systolic murmur transmitted to the left shoulder and to the back, best heard at the spine of the scapula. The liver and spleen were slightly enlarged. There was slight edema of the ankles. Blood examination showed hemoglobin, 110 per cent.; red blood-cells, 7,460,000; white blood-cells, 15,000. *x*-Ray of the chest confirmed the diagnosis of pulmonary tuberculosis. The sputum was positive for tubercle bacilli. Electrocardiographic study gave no assistance in the diagnosis of the cardiac lesion. The patient died September 5, 1922. The diagnosis was chronic pulmonary tuberculosis, with a congenital heart lesion, probably pulmonary stenosis. Necropsy the following day showed advanced pulmonary tuberculosis and the following cardiac findings:

The heart was enlarged, weighing 420 grams. There was hypertrophy both of the left and right ventricles. The pulmonary orifice was narrowed

(circumference 3 cm.). Two thickened and distorted pulmonary cusps were present, with vegetations on the posterior cusp extending into the pulmonary artery. Below the aortic cusps and anterior to the undefended space of the ventricular septum was a foramen measuring 2½ cm. in diameter. The foramen ovale also was patulous.

The following clinical case probably illustrates the same type of defect:

S. S., a white girl, aged fourteen, who was admitted to the service of Dr. S. Solis Cohen, at the Jefferson Hospital, on March 28, 1925, had shortness of breath, marked cyanosis, and clubbing of the fingers. The family history was unimportant. She had whooping-cough at the age of three and measles at five, both of which were uncomplicated. At ten she had influenza, with fever for three weeks, and was in bed for two months; she made a very slow recovery. Later an abscessed tooth was removed. Menses had not yet been established. The bluish discoloration of her skin was first noticed when she was about one year old, and the clubbing of her fingers had been noted at the age of two. She always became dyspneic and more cyanotic on exertion.

Physical examination showed a dwarfed child, chin tilted forward, pigeon breast, and bilateral congenital dislocation of the hips. She was markedly cyanotic and there was considerable clubbing of her fingers, but not of her toes. There was a harsh systolic murmur in the pulmonary area and over the upper sternum, heard less distinctly down the left border of the sternum. No thrill could be made out. Both aortic second sound and pulmonary second sound were present. The Roentgen ray of the heart was interpreted as indicating a possible widening of the aorta to the right; otherwise the heart shadow seemed normal. The electrocardiogram showed right ventricular preponderance and auricular hypertrophy.

The clinical diagnosis was congenital cardiac defect with venous-arterial shunt; probably pulmonary stenosis, dextroposition of the aorta, and defect of the ventricular septum.

The patient is living and enjoying fair health.

The most typical instances of congenital cyanosis with bluish discoloration of the skin becoming pronounced on exertion, clubbing of the fingers; dyspnea and cyanotic attacks are seen in the many cases in which the anomaly referred to is present. In typical cases, therefore, we have the characteristic congenital cyanosis associated with a prolonged harsh, rasping, or blowing murmur, pronounced at the base in the pulmonary area, but often heard over the whole cardia. A thrill in the same area and of the same time is frequently associated. The pulmonary second sound is usually weak or absent, contrasting with patulous

ductus arteriosus, in which pulmonary accentuation is the rule. In the majority of instances these findings, with increase of the cardiac dulness to the right and the symptoms of pronounced congenital cyanosis, such as clubbing of the fingers, polycythemia, and splenomegaly, make the diagnosis fairly easy. Such patients usually die in childhood, but many reach early adult life and die not of the cardiac lesion, but of pulmonary tuberculosis. Another not infrequent termination is from bacterial endocarditis developing at the seat of the defect.

And now, to direct your attention to the other and more important group in which I am chiefly interested.

NON-CYANOTIC GROUP (ARTERIAL-VENOUS SHUNT)

This group is composed of three main defects: (1) Patent ductus arteriosus; (2) patent foramen ovale; (3) defect of the ventricular septum. As you can readily see, these defects are closely related anatomically in that they represent circumscribed openings between the right and left sides of the heart (considering the aorta and pulmonary artery as continuations of the left and right ventricles). Under such circumstances we have been led to believe from morphologic findings that the passage of blood is from the left side to the right, *i. e.*, arterial into venous blood, thereby putting strain upon the right heart, but giving no cause for cyanosis, the arterial oxygenation being normal.* *Perhaps the greatest misconception in regard to congenital heart disease in the minds of the medical profession has been the association of cyanosis with this group of disorders.* Individuals with such defects are likely to live out a normal span of years, but an important feature of their condition is that a change of pressure in the lungs may convert the arterial-venous shunt into a venous-arterial one, with the resultant production of a transient or terminal cyanosis.

* Holman, in recent studies of certain types of congenital heart disease interpreted as intracardiac arteriovenous and veno-arterial fistulæ (Bull. Johns Hopkins Hosp., 36, 61–80, January, 1925; Arch. Int. Med., 36, 516–529, October, 1925), records cases of patent ductus arteriosus in which he believes the circulation through the defect was from right to left, *i. e.*, venous-arterial shunt.

Striking physical signs and absence of symptoms are the characteristic features of this group. A peculiar harsh murmur of unusual rhythm and intensity, often accompanied by a thrill, situated to the left of the sternum, in the first or second interspace, or over the middle of the precordium, and in many instances associated with evidences of dilatation of the pulmonary artery are the most important features of this non-cyanotic group. Dilatation of the pulmonary artery is to be considered as a functional consequence of the increased pressure produced by the connection between it and the aorta or between the right and left chambers of the heart. Such dilatation may be determined by percussion evidence of Gerhardt's dulness, *i. e.*, a ribbon-shaped area of dulness in the first and second interspaces to the left of the sternum, by an accentuation of the pulmonary second sound, and by fluoroscopic and *x*-ray findings of a marked bulging of the pulmonary arc. The electrocardiogram is not apt to be helpful in the diagnosis of these defects unless unusual strain on the right side of the heart has caused a preponderating hypertrophy of that side. Lewis has stated that in uncomplicated patency of the ductus arteriosus the curves should be normal. Elsewhere he has mentioned exaggerated amplitude in several leads of the electrocardiogram as an important sign in congenital heart disease.

Thus, we see that the diagnosis of a defect belonging to this non-cyanotic group is usually readily made. As a rule, the defect is discovered in childhood by the family physician who is attending for some unrelated condition; sometimes it escapes attention until adult life and is discovered during examination for life insurance. Rarely, in early life at least, do heart symptoms lead to its discovery. These facts emphasize the functional integrity of the circulation under such circumstances. Too often the attending physician terrifies the family of such a child with the statement that grave heart disease is present and the prediction that its years are numbered, basing his belief on the loudness of the murmur and the intensity of the thrill, whereas, in truth, loud murmurs and intense thrills are often associated with the least harmful defects, *i. e.*, those imposing the least strain upon the heart.

Given then, (1) a young patient, with (2) no history of rheumatic fever or other illness commonly causing endocarditis; (3) absent or slight heart symptoms; (4) marked and peculiar murmur and perhaps thrill in the upper left precordium; and (5) good cardiac functional capacity, and the diagnosis of a congenital defect of the heart with arterial-venous shunt is practically certain.

The problem now is to differentiate the various defects of this group, and this should interest us not simply because it represents a nice problem in differential diagnosis, but more importantly because of the prognosis; the various defects impose different degrees of strain on the heart and are not uniformly subject to bacterial invasion.

PATENT DUCTUS ARTERIOSUS

In the fetus a connection exists between the pulmonary artery and the aorta which carries practically all of the blood entering the pulmonary artery into the general circulation. Under normal circumstances this tube becomes closed off and undergoes atrophy in the transition from fetal to extra-uterine existence. If it persists as a communication, it constitutes a real danger, both from the standpoint of strain upon the heart and because of the liability of the edges and the walls of the patent duct to bacterial invasion.

Patent ductus arteriosus, like the other defects of the non-cyanotic group, is usually symptomless, particularly in early life, and is recognized by its distinctive physical signs. Frequently it is associated with other defects, and then, of course, the physical signs are modified. While the clinical picture is definite in adults, it is not so in infants, and here we may have great difficulty in distinguishing patent ductus arteriosus from other defects of the group.

Adults with patent ductus arteriosus are usually anemic, and sometimes this anemia is very marked. As a rule, cyanosis is entirely absent, as is clubbing of the fingers and toes. If present, cyanosis is either very slight or transitory, appearing only on exertion or, like the form previously mentioned, may be terminal (cyanosis tardive).

Characteristic physical signs are present in the great majority of cases. A peculiar rough murmur, systolic in time or continuous (*machinery murmur*) with maximum intensity in the pulmonary area or just beneath the left clavicle, is the most important physical sign. This murmur is transmitted upward toward the left clavicle, and, depending upon its loudness, may be heard over the whole precordium and in the back. Accompanying the murmur may be a thrill of the same time, *i. e.*, either systolic or continuous. The pulmonary second sound is usually accentuated, and this is considered an important point in differentiating patent ductus arteriosus from pulmonary stenosis, in which the pulmonary second sound is often weak or inaudible. *Dilatation of the pulmonary artery* is the rule and this gives the signs already enumerated—Gerhardt's dulness and, under the fluoroscope, a prominent, actively pulsating pulmonary arc. Increased vascular hilum shadows also speak for pulmonary dilatation. Laboratory aids other than the *x*-ray are of little value in the diagnosis of this defect. I have already quoted Lewis to the effect that in uncomplicated patent ductus arteriosus we may expect a normal electrocardiogram.

A striking phenomenon occasionally observed is paralysis of the left vocal cord due to pressure on the left recurrent laryngeal nerve. This unusual cardiac complication is better known in association with mitral stenosis in which it first was thought to be due to the pressure of the enlarged left auricle upon the nerve, but more recently has been ascribed to the direct pressure of the dilated pulmonary artery. This likewise is probably the anatomic basis in patent ductus arteriosus.

Patent ductus arteriosus is frequently the site of a bacterial endocarditis. The vegetations occur on the pulmonary side of the communication and may extend down the pulmonary artery and involve the pulmonary cusps. The occurrence of such a lesion is a very dangerous complication, for the vegetations are easily broken off, to be carried into the lung, there to produce a suppurative bronchopneumonia.

Susceptibility to infection constitutes the great danger of this lesion, and is an important reason for early recognition and pro-

phylactic care of the unfortunate individual born with a patent ductus arteriosus.

Abbott[2] has shown that out of 67 cases of patent ductus arteriosus 15, or 22 per cent., showed a bacterial lesion. While bacterial endocarditis is usually responsible for the fatal termination, increased strain upon the heart may lead to failing compensation or a sudden paroxysm, such as a suffocative attack, may be responsible for death.

The following case is probably one of patent ductus arteriosus:

S. G., a white girl aged fifteen, was admitted to the Jefferson Hospital November 10, 1924, on the service of Dr. S. Solis-Cohen, to whom I am indebted for permission to publish the case. She complained of occasional attacks of dizziness. She had been a patient at Jefferson two years previously, at which time she had complained of pain in the back and dyspnea on exertion. During her stay in the hospital she was entirely comfortable, and since her discharge had felt well, with the exception of the occasional attacks of dizziness just mentioned. During the winter of 1924 she had two attacks of tonsillitis. Her heart lesion was discovered in childhood; she had been aware of it for a number of years, and was very apprehensive concerning it. She never had rheumatic fever or any other infection that might have been responsible for heart disease.

Physical examination on her recent admission to the hospital showed a thin, wiry, poorly developed girl, with no cyanosis and no clubbing of the fingers. The heart apex was in the fifth interspace, just outside the midclavicular line, and dulness on the right side extended just beyond the edge of the sternum. In the second interspace to the left of the sternum there was a marked, continuous murmur (machinery murmur) and a thrill, so close to hand and so intense that Dr. Abbott, who saw her with me, thought it might indicate a direct communication between the aorta and the pulmonary artery. On her admission to the hospital two years before the electrocardiogram was reported as normal, and the *x*-ray demonstrated a heart that was perhaps slightly enlarged, with the right side a little more prominent than it should be. Now, under the fluoroscope, the right side of the heart was prominent and the pulmonary arc exaggerated and actively pulsating.

In order to protect her from further throat infections tonsillectomy was advised, and large cryptic tonsils were removed under ether anesthesia. There was no cyanosis during the operation, and no marked variation in blood-pressure. She made a good recovery and is feeling very well at the present time.

PATENT FORAMEN OVALE AND OTHER AURICULAR SEPTAL DEFECTS

This defect, which is the commonest of the group of which I am speaking, is perhaps the least often recognized during life, due

both to the fact that it is often latent and likewise because physical signs, when they do exist, are not generally correctly interpreted.

Individuals who have a patent foramen ovale are usually of slight build, often of infantile development. Although frail and delicate, they are usually harmoniously proportioned, but they may have an associated spinal curvature. A very important point, possibly better mentioned with the *x*-ray findings, is *hypoplasia of the aorta.* This was noted many years ago by Abbott, and has been separately described in recent literature both by French and German observers. It is a definite part of the clinical picture of patent foramen ovale. The murmur of patent foramen ovale has been described as inconstant and variable. It may come and go and vary as to time, although it is usually systolic. A thrill is not often associated. Frequently the pulmonary artery is dilated, giving the signs already mentioned. In addition, the Roentgen ray may show the narrow aorta and a general enlargement of the heart, especially of the right ventricle.

The first symptoms of patent foramen ovale may develop following some condition which raises the pressure in the pulmonary circuit and converts an arterial-venous into a venous-arterial shunt, with an attending cyanosis. This may be transient and disappear when the cause of the heightened tension is removed, or may occur as a suddenly developed deep cyanosis in the course of cardiac failure or marked pulmonary disease, such as pneumonia, when it constitutes an important evidence of the presence of this defect. In the latter event it is apt to persist to the end as a terminal cyanosis. Patent foramen ovale, unlike patent ductus arteriosus, is not subject to bacterial invasion, and from the standpoint of infection can be disregarded. A very curious and dangerous phenomenon has been described with patent foramen ovale; that is, a paradoxic embolism in which the embolus, perhaps arising at some distant point, passes through the foramen and enters the general circulation.

A number of cases have been mentioned in the literature in which defects of the auricular septum have been associated with idiocy. Morse,[3] in a study of 100 cases of congenital heart dis-

ease from his private practice, noted mental deficiency in more than 10 per cent. of his cases.

The following case reported by Ziedler (Deut. Arch. f. Clin. Med., 131, 85, 1920) showed a terminal cyanosis, but indefinite physical signs. At necropsy there was a large defect of the auricular septum, with a narrow aorta.

Male, aged twenty-six; palpitation for twelve years. Five years ago pneumonia. Present illness: Admitted with heart trouble. Physical examination showed a small, slightly built, undernourished adult, slightly cyanotic. Thorax was narrow; epigastric angle sharp. Slight precordial bulging; vesicular breath sounds; apex-beat widely diffused in the fifth and seventh interspaces, most marked in the fifth interspace. Absolute dulness middle of sternum on right, one finger outside left midclavicular line. Loud systolic murmur at apex. P_2+. Aortic sounds somewhat impure. Liver three fingers below costal border. Spleen beyond costal border. No edema.

Progress: Cardiac dilatation much reduced by rest and digitalis; loud systolic murmur at apex, and impure loud second sound. P_2+. Pulse poorly filled, tension low; equal and regular. Two weeks later compensation was restored. One month after discharge there was a loud blowing mitral murmur.

Diagnosis of mitral insufficiency was made.

The patient was readmitted five years afterward. For nine months he had dyspnea and malaise. Now he showed marked cardiac symptoms. He was pale and cyanotic. Physical examination showed the heart 1½ cm. to the right of the sternal border, 2 plecimeter widths to the left of the midclavicular line; apex in the fifth interspace; systolic murmur at the apex; liver large; no edema. Two months later he developed pneumonia on the left side and died. The diagnosis was mitral insufficiency.

At postmortem was found a large interauricular defect, hypertrophy and dilatation of the entire heart, especially the auricles and right ventricle; dilatation of the pulmonary artery; a narrow aorta. Terminal cyanosis. No marked edema. Pulmonary artery 5 cm. in diameter, aorta 2½ cm. Pulmonary veins very wide; right ventricle very thick; tricuspid orifice admits 5 fingers; right auricle greatly dilated. Septum atriorum absent in greater part, represented by a rounded section 5 cm. in diameter, tapering off to a point above and below. In the lower left part it is of tendinous consistency. The left ventricle is much smaller than the right, the left auricle large; the mitral orifice admits 2 fingers.

VENTRICULAR SEPTAL DEFECTS (MALADIE D'ROGER)

Ventricular septal defects are frequently associated with other anomalies, and rarely do they occur alone. They are located, most commonly, directly beneath the aortic cusps and just anterior to the undefended space. The communication permits a shunt of blood from the left ventricle to the right, which has

been evidenced by a patch of fibrosis or a collection of vegetations on the opposite wall of the right ventricle. However, from the standpoint of strain, this type of defect in many instances might be disregarded, as it interferes in no way with perfect cardiac function and is consonant with a long and healthy life. *The importance of defects of the ventricular septum, and the danger is not, therefore the strain upon the heart, as in anomalies of the auricular septum, but the liability of vegetative endocarditis about the edges of the defect.*

These defects, probably more than any other in the noncyanotic group, are symptomless; indeed, the French (Laubry and Pezzi[4]) have applied to them the term "functional silence." They are recognized by their distinctive physical signs. A harsh, even murmur filling the entire systole, accompanied by thrill in about half the cases, situated over the middle of the sternum or in the third or fourth interspace to the left of the sternal border, is the most frequent and quite often the only evidence of this defect. A valuable lesson to be learned is that small defects, causing little or no strain upon the heart, and thus being of little functional importance, may give rise to the loudest murmurs. Because the defect causes little strain upon the heart, the usual phenomena resulting from dilatation of the pulmonary artery are not so common as in the other anomalies of this group. The pulmonary second sound is present, but not accentuated as a rule. The *x*-ray shows a normal heart shadow with no exaggeration of the pulmonary arc. This is true of the smaller defects. With larger ones, allowing a larger shunt of blood and consequent strain, these phenomena may be present. Under such circumstances, dilatation and hypertrophy, chiefly of the right ventricle, occur, and Vaquez and Bordet[5] describe in such cases a typical *x*-ray picture of a rounded heart having a blunt apex.

Case Report: Probable Ventricular Septal Defect.—R. B., white male, aged thirty-seven, consulted me on November 27, 1924, complaining of pain over the precordium, heart-burn, belching, and sleeplessness.

His family history was negative. He had always been a healthy boy. At the age of seventeen he had a bicycle accident, which was not very serious, but he attributed his heart trouble to that. At any rate, it was at this time

that attention was called to his heart, and for a few months he presented the symptoms above mentioned. Then he improved, came to America, and was well for a year; at which time, following an emotional upset, he again developed symptoms. He placed himself under the care of a physician of renown, who informed him that he had a congenital defect of the heart, and that it would in no way interfere with a long and healthy life. For the last eight years he had been quite well. Early in November, 1924 his mother died, and since then he had been considerably upset.

He was a rather dull-looking, short, stout man. Physical examination, with the exception of the cardiac findings, was unimportant. Examination of the heart showed a long-drawn-out, even systolic murmur and thrill in the third interspace to the left of the sternum. The murmur was less distinct in the fourth and fifth interspaces to the left of the sternum, but could be heard all over the precordium and in the back on both sides. The aortic and pulmonary second sounds both were well heard. Heart dulness seemed slightly increased to the left. Fluoroscopic examination demonstrated a rather broad heart with a blunt apex; but there was no evidence of an enlarged pulmonary arc. The electrocardiogram was within normal limits.

The long history of a heart lesion (twenty years) in a patient aged thirty-seven with occasional upsets and quick recoveries, the lack of a rheumatic history or other infection likely to cause endocarditis, the absence of cyanosis and clubbing, the presence of a long-drawn-out, harsh systolic murmur and thrill in the third and fourth interspaces to the left of the sternum, with no evidences of dilatation of the pulmonary artery, and a normal electrocardiogram leads me to designate this as a congenital lesion, probably ventricular septal defect.

After reassurance regarding his physical condition and a short rest he improved and is free of symptoms today.

Although it was my purpose merely to acquaint you with some of the diagnostic considerations of congenital heart disease, I cannot leave the subject without saying a word concerning treatment. Under this head there is really only one phase of the subject to be discussed, and that is the prophylactic care of those suffering from congenital defects, because once there are evidences of cardiac decompensation, the treatment is exactly the same as in acquired heart disease.

Let us direct our attention again to the arterial-venous or non-cyanotic group—those cases with distinctive physical signs, but excellent functional capacity. As already stated, their

chances are good for a long and healthy life. Two dangers exist —*infection* and *strain*. The incidence of bacterial endocarditis in patent ductus arteriosus has already been given. For some reason, not understood, defects of the auricular septum are not subject to bacterial invasion, while infection of defects at the base of the ventricular septum (in Abbott's statistics) have occurred in 16 out of 40 cases, or 40 per cent. Bacteria, probably arising from focal infection, are implanted about the edges of the defect, and there flourish to produce large fungoid vegetations, which break off and form dangerous emboli. Death may occur from a fatal embolus or from the toxemia and exhaustion produced by the infection. Therefore, our first duty toward these unfortunate persons is to rid them of all sources of focal infection; our second duty is to protect them from undue strain, which may convert an arterial-venous into a venous-arterial shunt, with cyanosis and possibly dyspneic or suffocating attacks. Such strain may arise from great physical exertion or from lesions causing a sudden rise in tension in the pulmonary circulation.

Before closing I must repeat that prognosis in congenital heart disease depends not so much upon the intensity or the location of the murmur as it does upon the presence or absence of other symptoms. However, even with congenital defects producing marked symptoms, we still must be hopeful, for it is often remarkable how long such patients may live and how much they may accomplish.

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CLINIC OF DR. TRUMAN G. SCHNABEL

UNIVERSITY HOSPITAL

INTERNAL MEDICINE, ENDOSCOPY, AND CYSTO-URETHROSCOPY

WITHIN recent years endoscopy has assumed a more and more important rôle in the diagnosis and treatment of disease. The internist calls upon the endoscopist for all manner of help, and, in turn, the endoscopist looks to the internist for counsel and aid. It is to show this mutual relationship that we wish to present 3 patients for your consideration this morning, and in the course of their presentation to comment on certain matters concerning the diagnosis and treatment of their diseases. In a similar way we will show a fourth patient to emphasize this same mutual relationship between cysto-urethroscopy and internal medicine, as well as to again call attention to a urethral lesion with local symptoms occurring with tuberculosis elsewhere in the body.

The first patient was referred to us nine months ago with a chief complaint of pain in the epigastrium, coming on a half to one hour after food. She had occasional pyrosis and had vomited several times. She felt that it was meat that had been responsible for the vomiting. She complained of a lump in her throat having no relationship to the act of swallowing, indeed, she had no difficulty whatever in eating. She was forty-six years old and was passing through the menopause. She probably was 7 pounds under her best weight of six months previous. On physical examination she presented some oral infection and some mild evidences pointing to cardiovascular degeneration. She had a slight secondary anemia; 100 c.c. of gastric contents were obtained without difficulty by the single extraction method forty-

five minutes after an Ewald meal. The free hydrochloric acid titration showed 26, and the total acid value was 38. The occult blood reaction was negative. Pepsin was present and the microscopy of the gastric contents was normal. The urine and renal functional tests were normal. *x*-Ray examination of the gastro-intestinal tract showed the esophageal transit time to be normal for a barium buttermilk mixture. There was some slight six-hour gastric retention—a small constant duodenal deformity —a ptosis of the stomach and colon of mild degree, and some intestinal stasis. The bismuth capsule technic was not carried out.

She returns now with the story that she experienced considerable relief from symptoms after her first visits by taking modified milk and cream hourly feedings, together with vigorous antacid medication. This treatment was suggested with the thought that she might have a duodenal ulcer. Our follow-up in her case was unsuccessful. She further tells us that six months ago she resumed vomiting and has been having this experience with increasing frequency. Vomiting usually occurs soon after taking the evening meal. The vomiting is not sour. She feels that she is less likely to vomit after fluids than after eating solids. She has a continuous epigastric pain passing up behind the sternum and now is 21 pounds under her best weight. When an effort was made to make a test-meal study this time, the tube would not enter the stomach. *x*-Ray investigation showed that the bismuth buttermilk column was checked at the cardia, but after a time passed very slowly into the stomach. There was a widening of the esophageal shadow above, tapering off to a point below (Fig. 27). The shadow, as you may see in this film, does not seem to show any irregularity in outline, and makes one think of a so-called cardiospasm, or, as Dr. Jackson styles the condition, a preventriculosis. We then asked Dr. Tucker to esophagoscope the patient, and he reports finding a diffuse induration of the abdominal esophagus involving its entire circumference. On looking through the esophagoscope the lower end of the esophagus looked very much like the inside of a cone viewed toward its apex, and contact of the distal end of the esophagoscope with the

esophageal wall gave a sense of tough resistance to the operating hand. This funnel-shaped lower end of the esophagus with its indurated but non-ulcerated wall explains the absence of de-

Fig. 27.—Esophageal carcinoma shadow simulating that of preventriculosis.

formity in the *x*-ray shadow. The mucosa bled very freely. A biopsy shows the lesion to be carcinoma.

We have suggested a gastrostomy, which is only palliative. The patient refuses this advice, but will be compelled no doubt sooner or later to submit to this operation. This is, unfortu-

nately, the only advice we can give these patients, because the diagnosis of esophageal neoplasm is made too late. We were guilty of an investigative omission nine months ago when we failed to examine the esophagus with the bismuth capsule technic, and further when we did not secure an esophagoscopy. The smallest and mildest esophageal lesions interfere with the transit of a No. 0 bismuth capsule through the esophagus even when water is swallowed. We should have had these studies made on the strength of the story of a lump in the throat and the history that eating meat seemed to cause vomiting. Such an apparently insignificant recital is frequently the earliest evidence obtainable in neoplasms of the esophagus. Dr. Jackson, in his "plea for early diagnosis" in malignancy of this organ, quotes many of his patients as first complaining of "a slight queer feeling in swallowing," "a feeling of nervousness about starting to swallow," "a feeling of nervousness in the neck," "a feeling of cramp around the neck," "food sticking in the throat while eating in a hurry," "a feeling as of a lump rising in my throat," etc. When we will heed such seemingly trivial testimony on the part of our patients and then have esophagoscopy practised, then we will probably be able to present early cases of esophageal carcinoma to the surgeon, and he may be able to devise a satisfactory technic for early excision, or perhaps some satisfactory method for radiation treatment may be discovered. The usual text-book picture presented when dealing with esophageal malignancy is unfortunate, in that it deals with a late situation. We must ask our patients concerning the swallowing function, past or present, and proceed with investigation on the slightest suspicion. We should never delay until dysphagia, weakness, anemia, and loss of weight occur as items in the history.

This case illustrates the point that Roengten-ray examination may be inconclusive in the matter of diagnosticating carcinoma of the esophagus even when far advanced. The only real certain diagnostic method for this lesion seems to be esophagoscopy with a biopsy. This does not mean, however, that our patients should be rushed to the endoscopist before every other possible study has been made. It is the last investigation to be made after a

complete history has been taken, a complete examination of the nose, throat, larynx, and entire body has been experienced, urine, blood, and sputum have been studied, the blood Wassermann has been done, *x*-ray studies made for aortic aneurysm, mediastinal lesions, for the esophageal transit time with various media, for disease of the lungs and entire gastro-intestinal tract. The endoscopist rightly refuses to examine the esophagus unless he has information concerning all these findings. He must know whether disease elsewhere in the body may explain the patient's symptoms, whether it might be dangerous to pass the esophagoscope, or, if possible, what sort of a lesion he may expect to find in the esophagus itself. The internist is in a position to answer a number of questions preliminary to all endoscopic procedures, and should always completely study his patient before requesting an endoscopic consultation.

We wish to mention the esophageal bougie only to condemn its use. Mr. Tilley, again quoting from Dr. Jackson's article, points out that a bougie "may fail to detect any obstruction when the growth is small or even in advanced cases when rapid ulceration fails to produce stenosis"; "if obstruction is met with, the bougie affords no more than presumptive evidence of its nature," and "that fatal results have followed the use of the bougie." In our own clinic we no longer use even the rigid type of gastric tube when an esophageal lesion is suspected. There seems to be no objection to a flexible duodenal tube in such patients, although it, like the bougie, only yields presumptive evidence and only affords information when the lesion is highly obstructive, as is shown in our case.

In this connection we wish to suggest the use of the duodenal tube as a means of evacuating the esophagus when this organ presents retention for any reason. In the preventriculosis patients as well as in the esophageal carcinoma victim, whether before or after gastrostomy, much difficulty arises as a result of an associated esophagitis. If the esophagus is completely emptied each night and subsequently lavaged via a duodenal tube, the esophagitis is considerably allayed and much comfort is given to the patient. The swallowing function improves and a better sleep

is assured. The overnight esophageal retention, as in the case of gastric retention, serves to keep up the inflammatory process. These patients are instructed how to use the duodenal tube, and then they practice the esophageal evacuation and lavage at home before going to bed.

Many esophageal carcinoma patients pass for some time as being functional in origin, which is, of course, unfortunate. Such a feeling was held in our case before she came to this outpatient department. Squamous-celled endo-esophageal carcinoma is not a rapidly developing lesion, taking in some instances a number of years to progress to the obstructive stage. When, however, this occurs, events go rapidly, as our case illustrates. We must again emphasize that it is in the early stages of the disease that we must have these patients *x*-rayed and studied by the esophageal endoscopic method. Be loath here, as in all other fields of medicine, to label a patient as functional. The neurotic of today may be the obviously organic of tomorrow.

This case, then, is one in whom an accurate diagnosis of esophageal malignancy could only be made by esophagoscopy and biopsy. The *x*-ray shadow showed no filling defect. The case further serves to remind us of the fact that for a long time carcinoma of the esophagus presents no symptoms pointing to this organ, or at the most presents very vague ones, and that *x*-ray and esophagoscopy afford an only hope of eventually leading the way to a reduction of a 100 per cent. mortality in this disease.

Our second patient is a girl twenty-three years old, who complains of coughing and expectoration dating back to fourteen years. Prior to this time she had had a number of attacks of pneumonia. Ever since the last attack of this disease our patient has coughed up a cupful of "foul-smelling, yellowish-green," mucopurulent material every three hours during the day, and at night whenever turning on the left side or when lying on the back. A right lateral position was less likely to provoke coughing. The periodic attacks of coughing with the resultant evacuation of a foul-smelling sputum made her own life miserable as well as that of those about her.

Her morning temperature was $99\frac{1}{5}°$ F. and her pulse rate was 88. Physical examination showed her to be in a fair state of nutrition, she had clubbed fingers, a slight bilateral exophthalmos, and sclerotic tonsils. The left chest behind was relatively emphysematous, with no râles, while on the right side there were numerous râles of every description, and the breath sounds were distant and somewhat granular. The right base expanded less than the left one. The urine was normal, the blood-count showed a moderate secondary anemia, the white cells counted 8900, and the small mononuclear elements were relatively increased. The blood Wassermann was negative and repeated sputum examinations were reported free of acid-fast organisms. The *x*-ray showed an extensive opaque lesion in the lower right lung anteriorly with an associated interstitial pneumonitis (Fig. 28). Although this film we show you has been taken recently and shows the result of lipiodol injection of the lower right lobe bronchus, the extent and character of the lesion from the Roentgen-ray standpoint has not changed since her admission. The middle lobe bronchus drains the main lesion, and on bronchoscopy showed and continues to show much pus and granulation tissue. It was impossible on this account to inject the middle bronchus, and the bronchiectatic cavity, therefore, contains no lipiodol.

For six months Dr. Tucker has been aspirating this middle lobe bronchus and has been practising frequent local medication to its mucosa. A culture from this bronchus yielded a non-hemolytic streptococcus, the Staphylococcus aureus, and the Micrococcus catarrhalis. A vaccine containing these organisms has been used for the last four months. Postural drainage in the interval between vaccine and bronchoscopic treatments has been practised and the patient has been living under favorable hygienic conditions.

As a result, today, she has but one coughing attack in every twenty-four hours, when she produces only a half-cupful of much less offensive sputum. This is probably as much improvement as we can hope for in this patient. Bronchiectasis of long standing and of extensive size is a difficult situation to deal with, and only a very occasional case is really cured by any method.

About 50 per cent. of patients improve as our patient has with bronchoscopic aspiration, local medication, vaccines, forced nutrition, fresh air, rest, and postural treatment. Frequently they

Fig. 28.—Bronchiectatic cavity shadow with lipiodol injection of the lower right lobe bronchus.

seem to be arrested on one or all of the above methods, but often they revert to the old state of affairs. Especially is this the case if they experience some upper respiratory infection. Our patient

is well pleased and clinically is much improved. The bronchoscopic and *x*-ray pictures are, however, discouraging. An interesting bit of evidence comes from the patient herself when she reports much more improvement in her cough and the amount of sputum when enough of the vaccine is given so that she experiences a general febrile reaction.

Whether or not some surgical procedure should be tried here must remain for future events to decide. Our patient is in an excellent physical condition, and if she remains so it probably will be wiser to postpone surgical therapy. Artificial pneumothorax, phrenecotomy, and extrapleural thoracoplasty are the procedures to be thought of in this connection. In selected cases and in skilled hands each of these methods seem to be followed by happy results. The first two plans are only available in the absence of pleural adhesions and seem to be less formidable than thoracoplasty. All of these methods would still seem to be on trial, and their status in bronchiectatic therapeusis must wait for future judgment.

This case, then, is a more or less text-book picture of bronchiectasis, and shows the results that can be hoped for in about 50 per cent. of patients when the simpler methods of treatment are utilized. It is further evidence of the co-operative rôle to be played by the internist in the diagnosis and treatment of this disease.

The third patient is forty-three years old. At eighteen months of age he swallowed lye and subsequently developed a stricture of the esophagus. Up until about four years ago he was only able to take liquids by mouth. At this time gradual dilatation of the esophagus was begun in Dr. Jackson's clinic, and now he is able to eat a mixed meal. The patient, when referred to our clinic, weighed 211 pounds, which is a gain of over 60 pounds since the treatment was started. He complained of headaches and had a blood-pressure of 190 mm. for the systolic reading and 110 mm. for the diastolic pressure. His urine showed a tendency to a fixation of the specific gravity at about 1015, the phenolsulphonephthalein elimination in two hours was 35 per cent., and the blood urea nitrogen was 21 mg. per 100 c.c. of blood.

The headaches seemed at that time to have no other explanation than that they had a nephritic origin and that the nephritis was of the glomerular variety. What rôle his obesity played in the picture was problematic.

Today the patient comes back for this third visit. He now weighs 205 pounds and feels much better. He has had no headaches. We prescribed a diet low in caloric value with an especial limitation of the carbohydrates, fluid, and salt intake. Today his blood-pressure is 160 over 100. We do not feel that this treatment has influenced his blood-pressure or that it has been responsible for his clinical improvement. This, however, has been our observation: that the obese hypertension patient improves almost uniformly as his weight goes downward. We feel that when our patient loses more than he has already done he will be even better. The treatment of hypertension by limiting the fluid intake and prescribing a salt-free diet has not been universally accepted, still it does seem to be worth using in such cases. Perhaps its unpalatability for some patients tends to make it easier to reduce the total caloric intake, and in this way weight reduction is achieved, and perhaps also a reduction of the blood-pressure. We, of course, are not aiming in this patient to treat his hypertension *per se*, but it would seem that our occasional successes in this direction have been obtained in the obese after some weight reduction. In this patient we believe that the endoscopist's efforts have been marvelously rewarded, but that now having had a food debauche for a few years, he must curb his appetite and reduce his weight if he wishes to remain free of unpleasant symptoms. These directions and cooperation in this way will come from our medical dispensary and its dietitian.

The fourth patient came to us from the Cystoscopic Clinic, where he had been admitted for burning on micturition. He had never had gonorrheal urethritis. The urine showed a few shreds. The consultation slip indicated that cysto-urethroscopy had revealed many large lymphocystic lesions in the posterior urethra. On further questioning in our dispensary, it was developed that he was coughing with morning expectoration, that he had lost

weight, and on his first visit had a morning temperature of 99° F. On physical examination there was considerable impairment to percussion over the right supraspinous fossa, the breath sounds over this area were vesiculobronchial, and there was a fine shower of inspiratory râles after forced expiration. The sputum showed acid-fast bacilli.

Dr. Pelouze has called our attention to these lymphocystic lesions in the posterior urethra as evidence of tuberculosis elsewhere in the body. They are never primary urogenital tuberculosis, they never ulcerate, they remain as long as the initial focus is active, and disappear as the patient's health improves. There is usually some ardor urinæ, perhaps a morning discharge, with some shreds in the urine. In this clinic we have been able to confirm Dr. Pelouze's suspicions in a number of instances. The urinary symptoms quite frequently have been the only ones complained of, while in other patients, not very many, the appearance of the patient suggests tuberculosis. Dr. Pelouze practices some local urethral treatment and refers these patients for a tuberculosis regimen. We propose to have this patient listed for a State Sanatorium, and until he can be admitted will institute antituberculosis measures in his home. It is anticipated that if his general condition improves his urinary symptoms will also clear up.

The presentation of these cases, it is hoped, suggests the internist's functions as a consultant to the fields of endoscopy and cystoscopy, and, in turn, the consulting possibilities of the latter to internal medicine. The internist should not call upon his confrères in these special fields before he has very thoroughly studied his case and is in a position to give an optimum amount of information to the consultants. The internist must further put himself in a position so that he is able to co-operate therapeutically, and from time to time report to the cystoscopist and endoscopist concerning the patient's progress.

CLINIC OF DR. SHERMAN F. GILPIN

JEFFERSON HOSPITAL

NEUROSYPHILIS

WHEN we consider syphilis of the nervous system we usually speak of two forms of the disease—the vascular, interstitial, or exudative form, and the parenchymatous form. In the interstitial form we speak of cerebral, spinal, and cerebrospinal type, according to the part of the central nervous system which is involved. The disease attacks by way of the blood-vessels, and we speak of the lesion as a gumma which may be discrete as a gummatous tumor of the brain; or diffuse, as in the syphilitic meningitis affecting the coverings of the brain and cord. In the parenchymatous form we include paresis and tabes. In this form the nerve tissue itself is involved and destroyed. The cause of syphilis is Treponema pallidum, discovered in 1905. Its exact biologic nature is not known, but it appears to be a protozoan. As we study neurosyphilis clinically we are impressed with the idea of there being different strains of the spirochete producing different forms of neurosyphilis. This has not yet been demonstrated conclusively.

The Treponema pallidum is apt to settle in the perivascular tissues of infected organs. The lesion consists of small lymphocytes, plasma cells, and fibrous tissue. It may be so small as to escape the naked eye. Diagnosis may rest on the microscopic examination.

Case I is a type of the interstitial form. The patient is a man aged sixty-three years, who came to the hospital with retention of urine and inability to walk because of weakness of his legs. Examination shows that the pupils react normally. His knee-jerks are normal. There is no Babinski sign and no ankle-clonus. He denies venereal disease. We find that he has been in the hospital on two previous occasions, each time with spinal cord

symptoms. On one admission his spinal fluid Wassermann was plus 3; at the present time it is plus 2. On large doses of iodids and mercury by inunction he has rapidly improved, so that now he is able to walk about the ward. He evidently has a specific meningomyelitis, which condition he neglects as soon as he is sufficiently improved to leave the hospital, and with a subsequent return of his symptoms.

Case II is of the interstitial type; yet you will notice that the symptoms are much different from those of Case I. He walks with a slight spasticity. On standing he shows slight ataxia. He tells us that the first symptom he had was a slowness in starting the stream of urine. He has had no pain. His knee-jerks are increased and he shows Babinski sign on each side. His spinal fluid shows 20 cells and a positive Wassermann reaction. He is rapidly improving under mercury by inunction and the oral administration of iodids. He is the so-called Erb's type of spinal syphilis, this clinical syndrome having been described by Erb.

Case III, male, aged forty-five years, came to the clinic because of severe pain in the shoulders and arms, together with marked atrophy and weakness in the muscles of the same region. He was slightly ataxic in both gait and station. His pupils did not react to light and his knee-jerks were absent. He stated that he had a chancre twenty-two years ago, that he had a secondary rash, that the diagnosis of syphilis was made, that he was thoroughly treated with biniodid of mercury (he is a chemist and so is clear as to the drugs he has taken), and was in good health until four years ago, when he developed severe pain in the region of the upper abdomen. He was studied in a hospital, and this pain was thought to be due to some stomach condition. He states that he then went to an osteopath and was cured. The present condition has been coming on for the past seven or eight months. His symptoms are pain, loss of sensation, marked atrophy and weakness of the muscles in the upper extremities, and loss of reflexes in the lower extremities. The pupils are Argyll Robertson. The question is, Is this a case of the interstitial type of neurosyphilis or is it a case of tabes? The points against tabes are the marked sensory loss in the upper extremities and the marked wasting of the muscles, showing that there must be another lesion different from the ordinary lesion of tabes. Again, the history of a well-marked chancre with a secondary rash is the history which we usually do not find in tabes. We believe this case to be one of the interstitial type in which the membranes in the cervical region are involved and in which the exudate has impinged on the nerve roots and accounts for the severe pain which appears to be of posterior nerve root origin, and by its interference with the anterior nerve roots accounts for the loss of power and the wasting of the muscles. His spinal fluid Wassermann is plus 4 and shows 24 cells. He has now been under treatment for six weeks and shows marked improvement.

Case IV is a man forty-one years of age; came to the clinic complaining of weakness and numbness in both legs from the knees down. Examination

shows that his pupils do not react to light, that he has absent knee-jerks, and well-marked ataxia, both in gait and station. His spinal fluid Wassermann is plus 2. In 1922 he thought he was getting rheumatism because of sharp pains in the legs. Tabes was diagnosed in a London Hospital at this time. According to his statements his blood Wassermann was positive at this time. In April, 1923 he was treated in a hospital in this city by the intravenous injection of neo-arsphenamin. He states that his blood became negative after six treatments. In April, 1925 he was again given six intravenous treatments of neo-arsphenamin, with one Swift-Ellis treatment. The blood was found to be negative and he was told that nothing further could be done. He came here in June, 1925, complaining especially of unsteadiness in gait and station.

Case V, man, thirty-eight years of age, is the type of case that we see quite frequently in this clinic. He has no knowledge of having had syphilis; eight years ago he began to have pains in the legs which he describes as sharp and stabbing. He went to his family physician, who had a Wassermann examination done on his blood. The report was negative. In spite of this fact the doctor considered that he had syphilis, and gave him treatment for a period of one and a half years. This treatment, according to the patient, consisted in the injection of some medicament intramuscularly into the gluteal region. At the end of this period he went to a hospital dispensary, where he was treated for two and a half years. He states that the treatment consisted in the use of an arsenical intravenously and that he was given at least ninety treatments. During this time the pain has been severe, his ataxia continually increasing, so that he comes to this clinic walking with a cane and afraid to trust himself to go on the street alone because of his marked ataxia. We find on examination that his pupils still react slightly to light, that his knee-jerks are gone, that the ataxia of gait and station are so great that it is impossible for him to walk or to stand with the eyes closed unless he supports himself on a cane. His fluid Wassermann on admission was plus 4; his blood Wassermann was negative. He has been under treatment since October, and he now walks without his cane, going anywhere he pleases alone, has no shooting pains, and feels himself to be in good health. His fluid Wassermann at present is plus 2. He is evidently a plain case of tabes.

Case VI, a woman, fifty-seven years of age, I present as our star case of tabes. Ten years ago she came to the clinic, being assisted by her daughter, as she was unable to walk alone, her ataxia being so marked at that time. This was especially true getting on and off trolleys. At that time her examination showed typical pinpoint Argyll Robertson pupils, marked ataxia in gait and station, but knee-jerks still slightly preserved. The explanation of this is that her tabes was of the upper type, the lightning-like pain showing itself especially in the left arm and shoulder and the left side of the neck. Her fluid Wassermann at this time was plus 4 with 45 lymphocytes. At the time of her admission arsphenamin in any form could not be obtained because of the war, and so she was treated simply with mercury by inunction and with

drainage of her spinal fluid. She received in all forty lumbar punctures with complete drainage of her fluid. The time of treatment extended over one and a half years. At this time she had recovered from her ataxia, she had gained 25 pounds in weight, and was free of the lightning-like pains. Her spinal fluid Wassermann was negative. She has had no treatment since; her spinal fluid has been examined each year. Remaining in this condition for eight years we began to feel that when tabes was once cured, it remained so. However, we are disappointed, as we find on examination of the spinal fluid one week ago that she now has a Wassermann of plus 2. She presents no clinical signs at the present time to show a recurrence of the disease. However, she will be treated again until the fluid is brought negative. Examination at the present time shows the pinpoint pupils as ten years ago, shows her knee-jerks diminished as ten years ago, shows no ataxia in gait or station, and shows the patient in good general health.

Case VII. male, forty-seven years of age; married, has one child in good health. He complains of difficulty in walking and states that the trouble started two years ago. On examination we find both blood and spinal fluid show a strongly positive Wassermann, we find that his pupils do not react to light, that his knee-jerks are absent, that he shows marked ataxia in gait and station, and that he walks with a cane. He states that he has suffered greatly with sharp pains in his legs during the past two years. We note the difference between this case and Case V—this man is as ataxic in two years as Case V in eight years; this man shows a strongly positive blood Wassermann, while Case V, with a small amount of treatment, shows a negative blood. We find that this man is retarded mentally, while Case V shows no evidence of any mental abnormality. In other words, while Case V is a clear-cut case of tabes, this patient we believe has cerebral involvement and is a much more serious case. Our diagnosis in this case is taboparesis, and our differentiation from tabes is because of the more rapid onset of symptoms and because of the mental involvement. We speak of him as a case of taboparesis, distinguishing him from a case of paresis because of the symptoms which so closely resembles tabes. As far as the progress and prognosis of his condition are concerned, it does not differ in any way from any other case of paresis.

Case VIII. male, age forty-five; married; no children. He began to fail in health three years ago. Patient is brought to the hospital by his wife because he is unable to work, because his speech is becoming so thick that she cannot understand him, and because mentally he is unable to take care of himself. Examination shows that his pupils do not react to light, shows a marked tremor of his lips, tongue, and fingers, an ataxic gait and station, and absent knee-jerks. His speech is of a dragging, slurring, drawling character, which it is impossible to understand. Both blood and spinal fluid are plus 4. This man presents the physical signs and shows the mental loss of a case of paresis. I show him to you because of the effect that has been produced on him by treatment.

Now, the remainder of the clinic, we will discuss the treatment of neurosyphilis. In the cases of the interstitial type of syphilis in which the tissues are involved through the blood-vessels it is very easy to use our iodids, our mercurials, our arsenicals, our bismuth, or whatever antisyphilitic remedy we may favor, and the specific germ can readily be reached. You notice the improvement in Cases I and II simply with the use of mercury by inunction and iodids by mouth. In the cases of the parenchymatous form we find we have a much harder problem as to treatment. We find that we can give mercury by inunction or by whatever method we choose to give it; we give the arsenicals intravenously, and for some reason our drugs appear to have no effect on the continued development of the disease. It may be that in the later stages it is difficult for the medicament to penetrate the blood-vessel walls because of endarteritis and perivascular fibrosis. A great many different methods in the use of drugs have been developed in the last fifteen years, but no method has been found to be specific in the cure of parenchymatous syphilis of the nervous system. The method we have employed in this clinic since 1914 has been the use of the arsenicals intravenously and mercury by inunction, together with systematic drainage of the cerebrospinal fluid by lumbar puncture. This has given us such satisfactory results that it has become our routine treatment. In the technic of this treatment a lumbar puncture is first done, the spinal fluid withdrawn, as large an amount as will readily flow, usually from 30 to 60 c.c.; the patient is then given an intravenous injection of some form of arsenic, maybe sulpharsphenamin, neo-arsphenamin, or tryparsamid. In the use of arsenicals we prefer to give a moderate sized dose, such as 0.6 gr. of sulpharsphenamin or neo-arsphenamin and 3 grams of tryparsamid. Case VI is an example of treatment by the use of mercurials alone with drainage of cerebrospinal fluid. She has had eight years of good health, with a negative Wassermann reaction during this time. Case V is a case typical of this clinic; he had been treated thoroughly with mercury and with arsenicals, but still his spinal fluid remained plus 4. His ataxia continually increased and he was suffering greatly from his

lightning-like pains. In this clinic he was first given a series of sulpharsphenamin intravenously, each one with drainage of the spinal fluid. During his rest period of six weeks he was given mercury by inunction and his spinal fluid was drained once a week. He then had a second course of sulpharsphenamin with drainage of his spinal fluid, then a second course of mercury by inunction with drainage of his spinal fluid. At the present time he is taking a third course of sulpharsphenamin intravenously with drainage of the spinal fluid. He has had altogether twenty-four treatments, each treatment with drainage of the spinal fluid. You will notice the marked improvement and that now he is able to walk with comparatively little ataxia and that his fluid Wassermann has dropped from plus 4 to plus 2. Case IV is a similar case. He had been treated by way of his blood-vessels, but he had never had drainage of the spinal fluid until he came to this clinic. He is now improving. Case VII—that of taboparesis—has been treated in this manner. He has improved both mentally and physically. Serologically he is still plus 4. Case VIII has been treated by spinal drainage, followed by the intravenous use of tryparsamid. He had one series of ten treatments, followed by a rest period, during which he used mercury by inunction and during which time his spinal fluid was drained once weekly. He is now taking the second series of tryparsamid treatment. His speech has improved so that we can now understand him when he speaks his name; he has gained in weight; his general health is much better; he has been back to his work as a laboring man for the past three months. In other words, he is having a remission in the course of his disease. Serologically, he has not improved. His Wassermann is still plus 4. There is one caution to be observed in the use of tryparsamid; this drug seems to have a special affinity for the optic nerve, and it should be given to patients only after a thorough examination shows the optic nerve to be in normal condition. In some clinics the results from its use have been bad, as far as the optic nerve is concerned, and as high as 2 and 4 cases of blindness in a series have been reported. From our experience we cannot see any advantage in the use of tryparsamid over

sulpharsphenamin. There are other methods and styles of treatment which come and go. A number of years ago the Swift-Ellis treatment was used a good deal, and some men rely on it at the present time. In this treatment the patient is given an intravenous dose of neo-arsphenamin—in a few minutes his blood is taken, and about 40 c.c. of serum is separated from the blood and the serum sterilized. The next day a lumbar puncture is done and the fluid drained, and the salvarsanized blood-serum, in a proportion of about 4 parts blood-serum to 6 parts of normal salt solution, is injected into the arachnoid sac. Some men still believe they secure good results with this treatment; and some men state that the only result they secure from drainage of the spinal fluid is that the patient has a headache. In our experience this very rarely occurs in a case of tabes or paresis. We drain our patients in the out-patient clinic and allow them to go home in one or two hours.

A treatment that in recent years has attracted attention is the use of malaria. A patient with paresis, for instance, is inoculated with malaria. If the inoculation is successful, the patient develops chills and fever and runs a regular course of malaria. This is allowed to continue until the patient has had a number of attacks of fever, and any time it is wished to control the attacks the patient is given quinin. Reports from the various institutions, both here and in Europe, have been favorable. The most they claim is a remission of the disease. The cases treated in the Philadelphia Hospital by this method do not show results that would make one enthusiastic about the treatment. We must be careful in choosing the cases for this treatment. Syphilis in itself is a severe disease; malaria is another severe disease. It is rather dangerous to give a patient, very ill with paresis, a disease which in itself can make him very ill; and the patients chosen for this treatment must be ones in good condition; otherwise the malaria will only carry off the patient. As far as we can judge by reports, the remissions produced by this form of treatment are no more frequent or more prolonged than in the ordinary method of treatment by the use of mercury and arsenicals, with drainage of the spinal fluid. The longest remission in a case of

paresis treated by drainage of spinal fluid—to my knowledge—is ten years, and the patient is still in good health. The longest remission in a case of tabes is the one I have shown you, lasting eight years. The treatment is much simpler and much safer to carry out, and is much more convenient than is the treatment with malaria.

CLINIC OF DR. JOHN H. ARNETT

UNIVERSITY HOSPITAL

CARDIOVASCULAR SYPHILIS

Case I.—A woman of twenty-two applied to the Dermatological Dispensary for treatment of a rash which she first noted two weeks ago. No symptoms are complained of except a few vague muscular pains and a little nervousness. Her cardiovascular examination is negative except that there is a soft systolic murmur heard over apex of the heart. The temperature is 99.5° F. The pulse rate at rest is 90, after mild exercise it increases to 126, and after two minutes is 96. The electrocardiographic tracing is normal and the orthodiagram shows the heart and aorta to be of normal size. The skin shows the typical eruption of secondary syphilis, and mucous patches may be seen upon the tonsils. The diagnosis is obviously secondary syphilis. My reason for presenting this case is for a consideration of the cardiovascular system in early syphilis.

Most cases of secondary syphilis which I have examined have not shown any more convincing evidences of cardiovascular involvement than the case before you. Often a murmur is audible over the mitral or pulmonic area, the pulse rate is often above normal while at rest, and may not return to normal as quickly as it should after exercise; there may be a little palpitation. The evaluation of such vague signs as these is extremely difficult. It has led to a certain conflict of opinion, some writers emphasizing the early selectivity of the Spirochæta pallida for the cardiovascular apparatus, while others regard the signs merely as reactions of the organism to a systemic infection. Without wishing to enter too deeply into this somewhat academic discussion, there are several points which seem worthy of emphasis in this connection. There is good reason to believe that during, if not before, the appearance of the secondary rash, the spirochetes invade the cardiovascular system. However, serious cardiovascular complications during the early stages of

syphilis are extremely rare (very rarely, for example, do we see secondary syphilis at the autopsy table, and if we do see it, generally death has been due to some other cause than cardiovascular syphilis).

Let us for a moment apply to patients with secondary syphilis the same criteria of cardiac involvement which would be applied to those suffering from any other disease in which cardiac complications were feared. In such a disease we would look for an increase in the size of the heart, the development of a murmur, changes in the cardiac rhythm, signs of circulatory embarrassment, abnormalities of the electrocardiogram, and tachycardia out of proportion to the fever. Few of these signs of cardiac involvement have been present to a noteworthy degree in the cases of secondary syphilis which I have examined.* In comparison with a non-syphilitic control group the cases with secondary syphilis proved to have about the same relative cardiac size by percussion and *x*-ray, and no striking changes in the electrocardiographic tracings. In no case was obvious circulatory embarrassment present, while the only arhythmia noted was extrasystolia, which occurred once each in the secondary syphilitic and control group. Murmurs were present with approximately equal frequency in both groups. In this connection I should like to emphasize the frequency with which soft apical and basal murmurs occur in otherwise normal persons. McKenzie and Ayer[1] found such murmurs in 27.8 per cent. of the college men studied by them, and Thayer,[2] in a group of school boys found murmurs in 60 per cent. In my own control group of 76 women, approximately 45 per cent. showed systolic murmurs, usually best heard over the pulmonic or mitral valve areas.

One divergence of the syphilitic group from the controls was the presence in the former group of a greater number of cases showing a prolonged tachycardia after exercise and a greater number of cases in which the pulse rate at rest was over 100 per minute. This finding has been noted by other observers, who have been inclined to view it either as an evidence of cardio-

* Data soon to be published.

vascular involvement or as a nervous phenomenon. Whatever the explanation may be, I have the impression that the amount of cardiac damage incident to syphilis in its secondary stage is by no means great, nor to be compared with that which would be found in a group having, let us say, rheumatic fever, where, according to Swift,[3] there was auscultatory evidence of cardiac involvement in 72 to 93 per cent. of 81 cases studied, while 93 per cent. showed changes in the electrocardiogram.

Case II.—A woman of forty, while attending the gynecological dispensary for treatment of symptoms presumably due to an ancient pelvic inflammation, was found in the course of the routine examination to have a positive Wassermann reaction of the blood. She says that she becomes readily dyspneic on exertion. She does not recall having had a rash since she had measles as a child, and states that she has never had a genital lesion, although she has suffered for many years with leukorrhea. She has had occasional sore throats, but no noteworthy illness. Physical examination shows a healthy looking colored woman, 160 cm. in height, weighing 63 kilograms. The apical impulse of the heart is forcible and is displaced beyond the midclavicular line. By percussion both the heart and the aorta appear wide. Dr. Pancoast reports that her orthodiagram gives the following measurements:

Width of aorta, 7.3 cm.

M. L. plus M. R. (transverse diameter of the heart), 13.7 cm.

Chest, 23 cm.

The width of the heart shadow, therefore, is 60 per cent. that of the thorax, indicating considerable cardiac enlargement. The width of the aortic shadow, it will be noted, is likewise definitely above normal. Auscultation reveals a soft systolic murmur over the second interspace to the right of the sternal border; the murmur is transmitted into the right carotid artery. The second aortic sound has a ringing quality suggestive of hypertension, yet her blood-pressure is only 128/86.

The fact that the blood-pressure in this case is normal is of particular importance, since if hypertension were present, this might in itself explain the widening of the heart and aorta and the accentuation of the second aortic sound. A systolic murmur heard over the aortic area is likewise a frequent accompaniment of hypertension. The records of 77 cases with hypertension as the primary diagnosis from the medical wards of the hospital showed that systolic aortic murmurs were recorded in 26 (34 per cent.); transmission into the vessels of the neck was noted in 8 (31 per cent.) of the 26 cases. Aortic widening (7 cm. or over)

was noted in 9, and accentuation of the aortic second sound in 46, or 60 per cent., of the group. Probably if the same attention had been directed to auscultation of the aortic area in this group as would have been given to a group suspected of having syphilitic aortitis, the percentage of aortic systolic murmurs would have been decidedly higher. However that may be, the combination of cardiac enlargement, aortic widening, accentuation of the aortic second sound, and a systolic murmur heard over the aortic area and transmitted into the carotids, is very frequently met with in cases of hypertension. These signs can only be taken as valuable evidence of syphilitic involvement of the aorta, therefore, in cases of syphilis *without* hypertension. Such is the case in this patient, so that with these physical signs in the absence of hypertension, with a positive Wassermann, a diagnosis of syphilitic aortitis is certainly justifiable. The diagnosis of syphilitic aortitis is difficult if not impossible to make where hypertension exists, unless evidences of aortic regurgitation or aneurysm are present.

Case III.—A patient in the Men's Medical Ward was admitted complaining of cough, shortness of breath, and swelling of the legs and abdomen. He states that these symptoms came on rather suddenly while he was performing his usual duties as a watchman. The family history and social history are unimportant, and no history of an initial genital lesion was obtained. Physical examination shows a white man, aged thirty-nine years, dyspneic, and tremendously edematous. Signs of congestion are present at the bases of the lungs, and the presence of ascites is demonstrable. The skin of the lower extremities is tough and brawny, but pits on firm pressure; the legs are swollen to twice their normal size. The scrotum and penis are very edematous. The pulse is weak and rapid; the heart and aorta are greatly enlarged and both a systolic and a diastolic murmur are heard over the aortic area. The blood-pressure is 124/40. The urine contains numerous casts and a cloud of albumin. The Wassermann reaction of the blood is strongly positive.

Obviously, therefore, we are dealing with a case of aortic regurgitation and cardiac decompensation probably of syphilitic origin. Since the albuminuria and casts might be due either to nephritis or to passive congestion of the kidney secondary to cardiac failure, renal functional tests have been made with the following results; the blood urea nitrogen is 11 mg. per 100 c.c.;

the phenolsulphonephthalein elimination is 40 per cent. in two hours. Apparently, therefore, the urinary findings are to be explained on the basis of passive congestion.

The treatment of this case should be directed first and foremost toward the relief of circulatory embarrassment, the latter being due in large part no doubt to the mechanical effects of anasarca. Tapping the abdomen is indicated and multiple inch-deep punctures of the legs in addition. The latter are to be preferred to the use of Southey's tubes because of the greatly thickened and indurated character of the skin. Such punctures will drain for days, resulting in a loss of gallons of fluid, and apparently seldom become infected if ordinary precautions are observed. Most patients with this degree of anasarca voluntarily select the sitting position, and since dependence of the legs favors drainage, they should be allowed to remain seated day and night while the leg punctures continue to drain. Digitalization should be rapidly accomplished by administering 5 c.c. of an active standardized tincture every four hours until digitalis effects are manifested either clinically or by means of the electrocardiogram. Digitalization can then be maintained by the daily use of smaller doses (1 to 3 c.c.) of the drug. If these measures are successful in overcoming the immediate peril of decompensation we will then have to decide regarding the treatment of the underlying condition responsible for this patient's decompensation. We have here a very definite problem presented. It would require boldness to the point of folly to administer intensive antisyphilitic treatment to a case recovering from such extreme decompensation as this, yet the fact that decompensation occurred while he was engaged in such a sedentary occupation as that of watchman makes one feel fearful of employing a policy of *laissez faire* with reference to his syphilitic infection. I think one might say without fear of contradiction that some form of antisyphilitic treatment will eventually be indicated assuming that the cardiac decompensation yields satisfactorily to treatment. The questions are, what form of treatment should be given, and when should it be commenced? Iodids in small doses can do no harm, and there is no objection

to giving gradually increasing doses, commencing with 0.3 gram of potassium iodid three times daily, as soon as digitalization has been accomplished. When the albuminuria and cylindruria subside the question of mercury medication versus bismuth must be considered.

The selection of the best drug for antisyphilitic medication is not always an easy matter in cardiovascular lues. In Case I there can be but little question that intensive treatment with mercury, iodids, and arsenicals is indicated. The more conscientiously such treatment is carried out in the secondary stage of the disease, the less will be the probability of cardiovascular lesions appearing later. Where the aorta has been involved by tertiary lues, as in Case II, there is room for a difference of opinion. Fear of arsenicals in the treatment of cardiovascular syphilis has given place to boldness in some clinics where cardiovascular lues is treated as intensively as any other syphilitic manifestation. This, in my opinion, is dangerous practice. While it is true that arsenicals are not contraindicated in aortitis, as was formerly taught, yet in our experience they should be used with caution and only after a thorough preparation with mercury. The first dose should not exceed the equivalent of 0.1 gram of neo-arsphenamin. At weekly intervals gradually increasing doses may be given if no ill-effects are noted. The equivalent of 0.6 gram of neo-arsphenamin should not be exceeded. In cases where the disease has not spread to the aortic leaflets sufficiently to produce well-developed aortic regurgitation, treatment along the above lines is often attended with considerable success. Keidel and Kemp[4] report that in 10 cases of uncomplicated syphilitic aortitis, where the patients cooperated sufficiently for satisfactory treatment to be carried out for one year or more, every case made a very distinct improvement, while several cases which had been treated intermittently or not at all grew worse or succumbed.

Still more problematic is the question of arsphenamin therapy in the more advanced cases of cardiovascular syphilis, those, for example, manifesting the peripheral signs of well-developed aortic regurgitation, those with aneurysm, or syphilitic myo-

cardial disease. Here arsenicals are not without danger, as witnessed by the deaths reported by Stokes,[5] Keidel and Kemp,[4] and others. On the other hand, mercury and iodids are believed by Grund[6] and others to be of little or no benefit in such cases. In this dilemma we may perhaps look to bismuth for assistance.

As regards spirochetocidal activity, bismuth stands midway between mercury and arsphenamin. Given (as it should always be) intramuscularly, its slower absorption renders its action less dangerous and more prolonged than arsphenamin. After a perusal of the literature, Grund[6] has failed to find any reference pointing to an untoward action of bismuth when used in patients with heart disease and an added syphilitic infection, or in subjects manifesting syphilitic heart disease. It must be remembered, however, that bismuth is capable of producing a Herxheimer reaction,[7] that the absorption of the drug from the site of its injection into the muscle is both slow and variable,[8] that considerable pain may occur at the site of the inoculation; gingivitis and stomatitis, while far less common now than in the earlier days of massive dosage, are still occasionally encountered, as is the bismuth line upon the gums. Like mercury, bismuth may produce renal irritation, though no reference to any case of permanent renal damage from this cause has been found by Hopkins.[9] Acute bismuth poisoning from therapeutic doses of the drug has been reported.[10] It will, therefore, be seen that in common with mercury and arsphenamin, bismuth possesses very definite limitations and dangers, but it also possesses distinct advantages in its more rapid action and higher spirochetocidal activity as compared with mercury, and its greater safety and more prolonged action as compared with arsphenamin. Bismuth would, therefore, appear the drug of choice in Case III. It must be said, however, that the outlook is almost hopeless under any form of treatment, where, as here, signs of well-developed aortic regurgitation in addition to decompensation are present. Decompensation due to syphilitic myocarditis without aortic regurgitation (as exemplified by Case IV) gives a decidedly more favorable prognosis.

Case IV.—A colored man, aged twenty-nine, entered the Men's Medical Ward complaining of difficulty in breathing, cough, and swelling of the legs. He first noticed these symptoms six months ago, but during the two months prior to admission they occurred with increased severity. He also noticed that his abdomen was increasing in size, producing a sensation of fulness often accompanied by abdominal pain. Inquiry into his past history showed no rheumatic fever, but he gave a history of gonorrhea five years ago and chancre one year ago. The latter was not treated and was followed by a skin eruption. He was a laborer by occupation, and had been a heavy drinker of beer and whisky. Examination at the time of admission showed a well-built, muscular negro, evidently in a state of cardiac decompensation. He was drowsy and dyspneic. The blood-pressure was 160/138. Passive congestion was manifested in the lungs by râles, but the note was resonant over the entire chest posteriorly. The most striking physical finding in this case was the extension of the heart 8 cm. to the right of the midline, the left border being normal. This was verified by *x*-ray, the shadow being interpreted by Dr. Pancoast as indicative of dilatation of the right auricle. There were signs of fluid in the peritoneal cavity, and the liver edge was felt 5 cm. below the costal margin. The legs were swollen and pitted on pressure. The jugular veins were seen to pulsate at a rate greatly in excess of that of the cardiac apex, which was counted at 125 per minute. An electrocardiogram showed auricular flutter to be present with an auricular rate of 250 per minute, and a regular 2 : 1 block. The patient was given 1 gm. of digitan in divided doses in the first nine hours. An electrocardiogram on the following day showed auricular flutter, with an auricular rate of 240, and a ventricular rate of 60 due to regular 4 : 1 block.

The Wassermann reaction of the blood was now reported strongly positive; consequently, mercury inunctions and sodium iodid were begun, while digitan was administered daily in small doses. The patient next developed a cardiac psychosis, refused food, and had to be restrained. This condition recurred intermittently for some days, during which his pulse continued regular with a rate of 63, but was feeble. An electrocardiogram made at this time showed a normal rhythm, P waves which were markedly deformed, T waves which were diphasic in Lead II and inverted in Lead III, and evidences of left ventricular preponderance. These findings and the otherwise unexplained cardiac decompensation, in conjunction with the unusual cardiac outline and bizarre arhythmia exhibited by this patient in the presence of a positive Wassermann reaction, were interpreted as indications of syphilitic myocardial disease.

Inasmuch as very little progress toward recovery of com-

pensation was apparent, it was decided to stop the mercury inunctions and to administer 0.05 gm. of potassium bismuth tartrate intramuscularly three times weekly. The improvement was rapid from this time on. On the following day the patient became entirely rational, and continued so for the remainder of his stay in the hospital. Four days later all evidences of passive congestion had disappeared, and three weeks later the patient was well enough to be discharged from the hospital.

It is difficult to estimate how much of this patient's improvement was attributable to the bismuth and how much to the mercury inunctions which he had received for four weeks prior to the exhibition of the bismuth. However, the impression was difficult to escape that the therapeutic results were attributable, in part at least, to bismuth medication; this impression was strengthened a few weeks later by an almost equally dramatic improvement in another case of syphilitic myocardial disease, treated, in this instance, with no antisyphilitic medication except bismuth.

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THE TREATMENT OF POLYCYTHEMIA VERA WITH PHENYLHYDRAZIN

POLYCYTHEMIA vera, also called Vaquez's disease or erythremia, is a chronic disease, characterized by persistent and absolute polycythemia and enlargement of the spleen.

Chronic cyanosis may be due to congenital or acquired heart disease with circulatory stasis, chronic pulmonary affections, poisoning by acetanilid, dehydration as in diabetic acidosis, and other causes. In these conditions there may be an increase of hemoglobin and erythrocytes above the normal. This is sometimes called polycythemia or, better, false polycythemia.

Differential diagnosis between true and false polycythemia is of the utmost importance, as methods of treatment directed toward the relief of the conditions producing false polycythemia are of no value in treating polycythemia vera.

For the treatment of polycythemia vera numerous methods have been advised. Of these, repeated venesections and Roentgen ray or radium exposures have enjoyed the greatest vogue.

Venesection will, of course, reduce the total blood mass, only to have it quickly return to its former level. It is, therefore, not applicable as a routine and continued procedure, although of undoubted value in an impending cardiovascular catastrophe.

Roentgen ray or radium treatment of the long bones and spleen is sometimes used with good effect, but with obvious limitations. As is the case with venesection, the effects of radium or Roentgen ray therapy are temporary More important is the fact that these agents are not *selective* in their action; conse-

quently, as the red cells are being reduced, there is coincident reduction of the polymorphonuclear leukocytes. This makes it necessary to stop treatment because of the probable serious effects of too marked a reduction in the leukocytes, which may occur before the red cells have been appreciably reduced. The samé and other objections may properly be raised to the use of benzol.

Phenylhydrazin has been used experimentally to produce secondary anemia in animals. Morowitz and Pratt,[1] in this connection, speculated as to its probable effect in polycythemia. In 1918 Eppinger and Kloss[2] first used the drug for the treatment of this disease, and reported 4 cases.

Futcher,[3] in a communication presented before the College of Physicians in Philadelphia in October, 1924, reported the results of treatment in 1 case in which phenylhydrazin had been used. Owen[4,5] subsequently published this and 4 additional cases.

During the past year we have had the opportunity to have under observation 2 patients suffering from polycythemia vera, both of whom have been treated with phenylhydrazin.

Both were first treated in the hospital in order to have daily blood-counts made, and other investigations, which will be referred to later.

During the time that Case I was in the hospital all of the hemoglobin estimations and the blood-counts were made by Dr. Stadie in the Department of Research Medicine of the University of Pennsylvania. Particular importance attaches to the hemoglobin estimations because they were made by a colorimetric method, based on the gasometric method of Van Slyke. This gives figures of much greater accuracy than those obtained by ordinary clinical methods.

In each case 0.1 gram of phenylhydrazin hydrochlorid was given daily by mouth, in Case I over a period of sixteen days, and in Case II over a period of twenty-one days. Subsequently, after leaving the hospital, treatment in each case was continued by the administration of the drug in doses of 0.6 gram to 1.2 grams about once a month.

Case I, male, aged fifty. Three years ago began to be troubled with intense burning of the eyes, for which he consulted several ophthalmologists, without relief. At this time he developed vertigo, with sudden attacks of intense headache, invariably accompanied by visual disturbances (scintillating scotomata). Bleeding of the gums was also described.

The writer confesses with humiliation that the blood was not counted at this time. This is especially liable to occur in polycythemia owing to the ruddy appearance of the patient, warranting the assumption that there is no

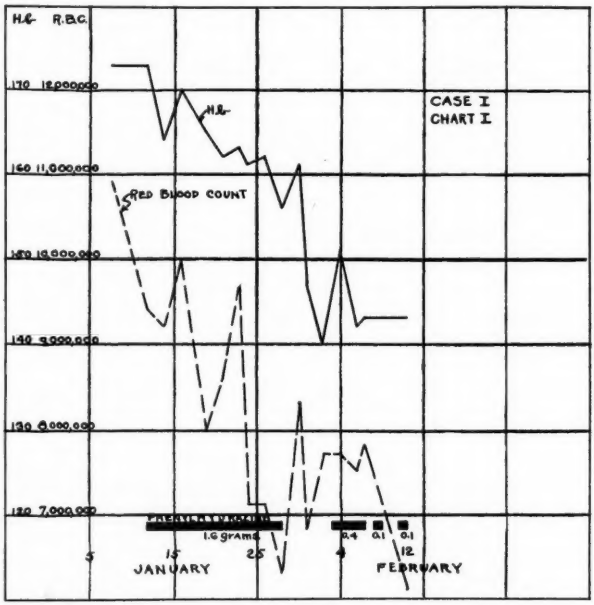

Fig. 29.—Case I. Daily record of hemoglobin estimations and erythrocyte counts during intensive administration of phenylhydrazin.

anemia. This should serve as one more plea for routine blood-counts on every patient, regardless of their appearance.

In March, 1924 a blood-count revealed 162 per cent. of hemoglobin, 10,760,000 red blood-cells, 18,400 leukocytes, and a cell volume of 75 per cent. A blood-count done in 1921 incident to a routine physical examination was normal. In view of the onset of symptoms in 1923 it is probably correct to assume that his erythremia began at that time.

In March, 1924 the outstanding findings on physical examination were the appearance of the skin and mucous membranes and splenomegaly. The blood-pressure was normal and there was no cardiac hypertrophy.

The color of the skin was not at all the cherry or rosy red which is most usually associated with this disease. It was definitely that of cyanosis, having a grayish leaden hue, resembling argyria, most noticeable in the face and hands; he had never, to his knowledge, taken silver in any form. There were dilated capillaries and venules on the face. The nail beds were much darker

Date	Dosage Grams.	Hb.	RBC
3/3/25	——	124	6,400,000
3/8		126	7,500,000
3/10/ to 3/15	0.6		
3/27		140	6,400,000
5/9 to 5/14	0.6		
5/16		135	5,720,000
7/7 to 7/12	0.6		
8/5		150	7,500,000
9/3 to 9/8	0.6		
9/25		150	8,600,000
10/5 to 10/10	0.6		
10/22		140	6,900,000
11/16 to 11/27	1.2		
12/12		125	7,000,000
12/17 to 12/26	1.0		
1/8/26		130	6,600,000

Fig. 30.—Case I. Subsequent treatment with phenylhydrazin and its effects on the hemoglobin and the erythrocytes.

than normal and bluish red. The conjunctiva was intensely red and velvety, and the gums were greatly congested and dark red.

The patient was referred to Dr. Pancoast for Roentgen-ray treatment, and during April and May, 1924 received eighteen treatments over the long bones and one over the spleen.

Treatment with phenylhydrazin hydrochlorid was begun in January, 1925.

Case II, male, aged forty-one. Was referred by Dr. Pancoast in March, 1925. His chief complaint was vertigo, which began in June, 1923. These attacks increased in frequency and severity, and were sometimes accompanied by blurring of vision, diplopia, and visual disturbances described as the effects produced by looking through a pin-wheel. Subsequently there developed headache, feelings of numbness in various parts of the body, faintness, and temporary amnesia and aphasia.

The outstanding findings on physical examination were the color of the skin and mucous membranes and splenomegaly. As in the previous case,

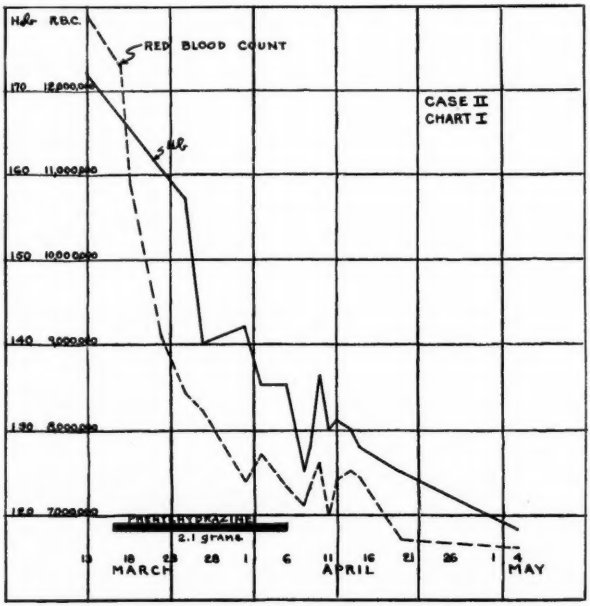

Fig. 31.—Case II. Daily record of hemoglobin estimations and erythrocyte counts during intensive administration of phenylhydrazin.

the blood-pressure was normal and there was no cardiac hypertrophy. The blood-count revealed 172 per cent. of hemoglobin, 12,900,000 red blood-cells, and 8500 leukocytes.

The skin was cherry red, a little dusky; the appearance so striking and so different from that of the patient before described that the diagnosis was obvious on sight. The nose, if possible, was more intensely red than the forehead and cheeks. The hands were of similar hue, but somewhat less intense than the face. In this case also the capillaries and venules on the

face were dilated and very conspicuous. The mucous membranes were deeply red and somewhat cyanosed. The nail beds were dusky red.

Treatment with phenylhydrazin hydrochlorid was started on March 16th.

Date	Dosage Grams.	Hb.	RBC
6/2/25		145	7,750,000
6/10 to 6/15	0.6		
7/6		—	6,640,000
7/18 to 7/23	0.6		
8/24		160	8,500,000
8/27 to 9/7	1.2		
9/17		—	7,200,000
10/13 to 10/22	1.0		
10/29		140	7,750,000
11/5 to 11/16	1.2		
12/7		130	7,200,000
12/16 to 12/27	1.2		
1/3/26		120	7,530,000
1/10 to 1/21	1.2		
1/28		120	7,900,000

Fig. 32.—Case II. Subsequent treatment with phenylhydrazin and its effects on the hemoglobin and the erythrocytes.

The following factors must be taken into account when phenylhydrazin is administered: 1 Its ability to produce hemolysis. 2. Its deleterious effect on the liver. 3. Its cumulative action. 4. Its effect on the leukocytes.

In order to obtain information concerning some of these factors, and also in order to have some check on treatment, hoping thereby to safeguard the patients to whom this drug

was being given, it was deemed advisable to study, both before and during treatment, the urobilin output in the urine and feces, the bilirubin content of the blood-plasma (van den Bergh test), and the possible effect on the liver by means of the tetrachlorphenolphthalein test. Regarding the latter, it was appreciated that it would only be of value in indicating extensive damage to the hepatic cells.

Case I prior to treatment had no urobilin in the urine; the urobilin output in the feces was normal (3200 units per day) and the van den Bergh test gave a normal reading (direct negative, indirect 0.6 unit). Subsequent examinations of the urine for urobilin during the time that phenylhydrazin was being administered daily were also entirely negative.

After 0.6 gram of the drug had been given the urobilin output in the feces was 6000 units per day, and after the administration of 1.7 grams it rose to 8100 units per day.

The van den Bergh test after 1.7 grams of the drug had been given gave a negative direct and 1.9 units indirect reading. The drug was stopped for five days, and after it had been resumed for three days (0.3 gram) the van den Bergh test showed a negative direct and an indirect reaction of 1.1 units, indicating that stopping the drug for five days, despite its resumption for three days, had caused a decrease in hemolysis.

The tetrachlorphenolphthalein test was done after 2 grams of phenylhydrazin had been given, and gave a reading within normal limits (10 per cent. of the dye was present in the blood-serum at the end of fifteen minutes, and none at the end of one hour). Similar studies were made in Case II, with approximately similar results. In neither case did jaundice develop at any time.

Wells[6] studied the pathologic anatomy of hydrazin poisoning on experimental animals, and concluded that its effects were remarkable, in that the drug only affected the liver. These changes were constant, consisting of fatty degeneration of the cytoplasm of the liver cells, beginning in the center of the lobule, the nucleus remaining intact. Küpfer's cells were not affected. When the animals were given enough hydrazin to make them

quite sick and were then allowed to recover, there was a gradual decrease in the amount of fat, and in two or three weeks the cells recovered their normal appearance. No evidence of increased connective-tissue overgrowth was observed. Wells contrasts the action of hydrazin with that of the poisons of eclampsia, acute yellow atrophy, and phosphorus, which affect first and chiefly the nuclei of the liver cells. He therefore concluded that in the case of hydrazin recovery to normal even after severe poisoning is more rapid and complete.

Levy[7] believes that the drug may cause cirrhosis of the liver, but he is uncertain as to whether it occurs primarily as the result of the action of the drug, or secondarily from hemolysis.

Owen very properly concludes that this risk is unknown and relatively insignificant compared to the results without treatment.

Bodansky[8] studied the action of hydrazin and some of its derivatives in producing liver injury, as measured by their effects on levulose tolerance. He used hydrazin, phenylhydrazin, acetylhydrazin, methylphenyl, diphenyl, and other derivatives.

Summarizing his results in brief, he found that phenylhydrazin produced great enlargement and hematogenous pigmentation of the spleen, fatty degeneration and hematogenous pigmentation of the liver, hyperplasia of the bone-marrow, and minor fatty changes in the kidneys.

Methylphenyl and diphenylhydrazin produced neither hepatic degeneration nor anemia.

Acetylphenylhydrazin produced marked anemia before marked destructive changes in the liver occurred.

Elimination of Phenylhydrazin.—This drug is very slowly excreted. For this reason it should not be employed in the treatment of erythremia unless its action can be carefully watched by frequently repeated blood-counts, and it should be discontinued before the blood-count reaches a normal figure, otherwise severe secondary anemia may ensue. In a case of erythremia under phenylhydrazin treatment reported by Taschenberg[9] the blood-count fell to 30 per cent. of hemoglobin, and 1,000,000 red blood-cells.

The urine is discolored a deep brown for some time, usually for about a week after the drug has been stopped. Tests for occult blood and urobilin were repeatedly negative. It is assumed that this discoloration is due to the excretion of the drug in some form.

Effect of Phenylhydrazin on the Leukocytes.—*Case I* had a leukocyte count of 12,900 before treatment. During treatment it varied between 8300 and 13,600.

Case II had a leukocyte count of 8500 before treatment. During treatment it varied between 6400 and 9300.

In neither of these cases did a sudden rise in leukocytes precede an abrupt fall in hemoglobin and erythrocytes, as has been observed by Owen, and regarded by him as an important indication for reducing or stopping the drug.

Case I under phenylhydrazin treatment for the past year has at the present time 130 per cent. of hemoglobin and 6,600,000 red blood-cells compared to a hemoglobin of 173 per cent. and 10,900,000 red blood-cells before treatment. He is distinctly cyanosed, but unquestionably less so. The mucous membranes are less congested, and the complaint of burning of the eyes has been almost entirely relieved. Headaches and sudden attacks of visual disturbance have occurred, but much less severe and more infrequent. The spleen remains enlarged.

Case II at the present time has a hemoglobin of 120 per cent. and a red blood-cell count of 7,900,000 compared to a hemoglobin of 172 per cent. and 12,900,000 red blood-cells before treatment. His skin is still abnormally red, but the color is not nearly so intense. After the first course of treatment he was relieved almost completely of his unpleasant symptoms. It has become apparent since then that his symptoms are almost as severe when his count is about 8,000,000 as they were when the count was much higher (12,000,000 or 13,000,000).

It is evident that from the standpoint of symptomatic relief in this patient his count should be maintained at a lower level than has been achieved. This will necessitate the use of larger doses, possibly because a tolerance to the drug has developed. The spleen remains considerably enlarged.

No untoward effects from the administration of the drug have been observed in either case.

Summary.—Two patients with erythremia have been treated with phenylhydrazin hydrochlorid.

Observations on the hemolytic effects of the drug have been made by repeated blood-counts, estimations of the amount of bilirubin in the blood-serum, and of the urobilin output in the urine and feces.

The possibilities of hepatic damage, fatty infiltration, and cirrhosis which may be produced by this drug have been considered.

Its slow elimination and its consequent cumulative action indicate caution in its use and its cessation before the blood-count reaches normal; otherwise severe anemia may ensue.

No marked effect on the leukocytes has been observed in these 2 cases.

Unfamiliarity with the drug and its possible untoward effects, particularly on the hepatic cells, has resulted in somewhat inadequate treatment. A monthly dose of 0.5 gram, as recommended by Futcher, has not been sufficient to maintain the blood-count at a normal level.

It is suggested that tolerance to this drug is acquired. This has been observed in its use in the production of secondary anemia in animals. Therefore it would seem that treatment over a long period of time would necessitate increasing doses.

As observed by Owen, other derivatives of hydrazin, particularly acetylphenylhydrazin, may be found to be equally effective in their hemolytic action, with much less danger of untoward effect on the liver. Further investigation in this field should be fruitful.

The writer wishes to express his appreciation to Dr. Stadie for the hemoglobin determinations and cell counts made in *Case I* during the patient's stay in the hospital; to Dr. Jonas for the urobilin estimations; to Dr. Glenn Ravdin for the van den Bergh studies, and to Dr. Kern for the tests for hepatic function.

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THE IMPORTANCE OF MEDICAL SUPERVISION IN HYPERTHYROIDISM

THE Out-patient Clinic devoted to diseases of the thyroid gland at the Hospital of the University of Pennsylvania is under the co-operative direction of representatives of the medical and surgical staffs. Every case suspected of having thyroid disease is here examined before a plan of treatment is decided upon, and, after conference, is either referred to the wards for admission or listed as an out-patient. Patients are also followed up through this department after discharge from the wards, so that we may obtain accurate information as to the results of treatment. The operation of such a clinic affords evidence of the value of medical supervision in hyperthyroidism, especially in hospital practice, and brings to mind the question of the rôle of medical management in this disease. Certain aspects of this subject will be considered in the present contribution.

It should be clearly understood that throughout the following discussion only those conditions now known as hyperplastic toxic (exophthalmic) goiter and toxic adenoma of the thyroid are included. These at the present time are considered to be definite clinical entities, affecting women more often than men, and constantly associated with elevation of the basal metabolic rate. It is entirely possible that future pathologic studies will force a change in the present classification of abnormal thyroids associated with toxic manifestations; for the purposes of this discussion, however, the generally accepted division into hyperplastic toxic (exophthalmic) and toxic adenomatous glands has been retained. Hyperplastic toxic goiter is very often accom-

panied by signs of vasomotor instability—flushing, sensations of heat, profuse sweating, especially of the hands and feet—extreme nervousness, apprehension and irritability, and tremors of the hands. The patients are usually, although not invariably, exophthalmic, with the classical associated phenomena of lid lag, widening of the palpebral fissure, infrequent winking, and disturbance of the power of convergence. Loss of weight is almost constant, and there is usually marked muscular weakness. Cardiac disturbances are often evident; tachycardia occurs early, and is often followed by arhythmias (auricular fibrillation and ventricular extrasystoles are commonest); hypertrophy of the heart undoubtedly occurs in some cases, although the frequency and extent of this is open to question; if untreated, the cardiac damage is usually progressive, ending in many instances in terminal cardiac failure of the congestive type. While the thyroid gland is usually diffusely enlarged, smooth, and rather firm, occasionally there is no goiter. In the so-called toxic adenomata there is not constantly a diffuse enlargement of the gland associated with the nodular growth; toxic symptoms do not usually supervene until late in the existence of the adenomatous enlargement, and the progress of the toxic syndrome is not characterized by the remissions which are so prominent a feature of the hyperplastic toxic goiter picture. Nervous manifestations may be wanting in toxic adenomata, and the only evidences of abnormal activity are often those referable to the cardiovascular system. Our discussion of medical management will apply only to the two types of thyroid disease mentioned above, and is in no way applicable to simple or non-toxic thyroid enlargements, adolescent goiter, or adenoma without toxicity.

Only a few methods of treatment in hyperthyroidism are considered worthy of trial at the present time. These are: (1) radiation; (2) surgery, which is usually considered to include ligation and subtotal thyroidectomy. Total thyroidectomy, followed, of course, by continuous use of thyroid extract, has recently been advocated by Gilman and Kay[1] in certain advanced cases, and 10 instances reported; further experience is necessary for its acceptance. (3) Medical treatment. These methods

must all be considered, individually or in combination, in planning the treatment of any patient with hyperthyroidism.

Roentgen-ray treatment has been relegated to a somewhat secondary position in most of the large clinics in this country, and is now used only as an occasional adjunct to surgery, or in certain cases in which surgery is not feasible. Even as a preoperative measure it has been largely supplanted by the reintroduction of iodin. Although there is still some difference of opinion as to the value of surgery,[2] the prevailing view at present is that partial thyroidectomy effects the most rapid and complete, if not the most permanent, amelioration of the symptoms of hyperthyroidism, and is the method of choice in the treatment of most cases. The evaluation of therapeutic methods is made difficult by the fact that spontaneous remissions or cures are not infrequent; and also by the fact that only a small number of cases[3] have been treated symptomatically and followed long enough to determine the results obtained without specific treatment. Definite lessening of symptoms and objective findings, beyond that to be expected in the spontaneous course of the disease, is necessary to establish the efficacy of any specific therapy.

With these facts in mind, let us consider briefly the position of medical treatment in hyperthyroidism at the present time. The ideal objectives of any form of treatment should be the relief of symptoms, the elimination of abnormal signs, a return to normal weight, the reduction of basal metabolism to the normal level, and the restoration of economic usefulness. The principles of medical management in general consist of: (1) complete mental and physical rest obtained, if necessary, by the use of sedatives. (2) A diet high in caloric value. The increased basal metabolic rate, and the fact that patients with hyperthyroidism actually expend more energy to perform a given amount of work than do normal individuals, result in the loss of weight which is characteristic of this disease. High caloric diets are necessary because of these increased demands on the tissues. (3) Restoration of the circulatory efficiency, effected chiefly by those factors which lower the basal metabolic rate—that is to say, rest and in certain cases the use of iodin—and often aided

by digitalis, which tends to improve cardiac function and to decrease the pulse rate if auricular fibrillation is present. The tachycardia is usually closely associated with the elevated metabolic rate, and is reduced concomitantly; it is significant chiefly as a manifestation of increased metabolism. (4) The treatment of coexistent diseases including the removal of foci of infection when they are obviously doing harm. (5) When there is definite indication for the prompt amelioration of symptoms and reduction of basal metabolic rate (as in preparation for operation or in emergencies such as the so-called crises), the administration of iodin, preferably as Lugol's solution.

Close co-operation between the internist and surgeon is of the greatest importance if good results are to be obtained from surgery. The frequent necessity for such combined supervision makes any classification of medical treatment rather difficult, but, in general, the indications for medical observation and treatment may be outlined as follows:

(A) In cases where surgery or Roentgen therapy is not indicated or is impossible: (1) Patients refusing these forms of treatment; (2) patients whose condition does not permit of operation or *x*-ray, especially those with evidence of crises of hyperthyroidism; and (3) certain early cases in which medical treatment offers a possibility of relief without the necessity of operation.

(B) In cases where medical supervision is an adjunct to operation: (1) For the detection and treatment of coincidental disease. (2) For the determination of the condition of the cardiovascular apparatus and the treatment of cardiac complications—in short, preparing the patient's heart to stand the strain of operation. This is one of the most important functions of the internist in his co-operation with the surgeon. (3) The treatment of postoperative complications, particularly cardiac insufficiency, respiratory infections, and acute thyrotoxic crises. (4) Re-examination of patients at varying periods after operation to determine the extent of improvement, with particular reference to the heart.

In our hospital experience the incidence of cases falling into

Group A has not been great. The use of the anoci-association technic precludes the mention of operation to the patient, and permission is rarely withheld by the family. Preoperative thyrotoxic crises have not been frequent in our wards, although they are undoubtedly an important cause of death, and contribute to cardiac damage. Kessel and Hyman,[4] in a series of 130 cases, ascribed 7 of their deaths to preoperative crisis, and reported good immediate results from the use of thyroxin in 5 mgm. doses intravenously in 3 desperate cases (further evidence, however, seems necessary for the acceptance of this method of treatment). Lugol's solution, in doses of 5 to 10 minims (0.3–0.6 c.c.) every four to six hours, is a very valuable aid in this emergency; sedatives, the administration of large amounts of fluids, complete rest, and the use of cold packs or ice-bags for excessive fever are of importance.

Although with increasing experience there are fewer and fewer cases of true hyperthyroidism left to be treated solely by medical means, nevertheless there still remains a considerable group in which surgery or *x*-ray should not be considered at first. This group is composed of patients in whom the signs and symptoms of hyperthyroidism, while quite definite enough to establish the diagnosis beyond question, are yet only moderate or slight; in these patients usually, although not constantly, the basal metabolism is only moderately elevated (below 30 per cent. above normal). In this connection it should be remembered that while elevation of basal metabolism is constant in hyperplastic toxic goiter or so-called toxic adenoma, the degree of such elevation is not necessarily proportionate to the severity of the intoxication or to the extent of organic degeneration, particularly myocardial damage. Many such individuals with so-called mild hyperthyroidism will show striking improvement or, indeed, permanent disappearance of symptoms if they are placed at rest, all sources of nervous and mental irritation removed, focal infection eradicated, and an attempt made to increase body weight by giving a high caloric diet.

The early diagnosis of hyperthyroidism is of great importance, and although few patients will apply for relief until the

disease is fairly well advanced, the increasing popularity of periodic health examinations should afford more opportunities for the detection of this condition before permanent damage has been done. Medical treatment should find in these very early cases an additional field of usefulness which will become greater as health examinations increase in frequency.

While iodin, as Lugol's solution, will very often cause marked improvement in the hyperplastic toxic goiters, such improvement is only temporary as a rule, and after reaching a maximum is followed by a slow return to the former condition, even though the drug be continued. The advisability of repeated courses of iodin in these cases has been considered by some, but there are not sufficient data extant to give any valuable information on this point. The tendency to spontaneous remission makes it difficult to determine the actual value of medical treatment in the mild cases. Progression or recurrence of symptoms, with the advent of signs of cardiac injury, are usually indications that medical treatment alone is not sufficient.

Although observation of cases untreated specifically has shown results comparable to those produced by surgery in the most skilful hands, operative treatment usually has the advantage of securing improvement more promptly and of arresting in many instances the progressive cardiac degeneration which is of such serious import. It should be noted in this connection that promising results have recently been secured by Dr. H. K. Pancoast and Dr. E. P. Pendergrass, of the Department of Roentgenology in this hospital, in treating a few selected cases with radium, although too few cases have been treated as yet to permit conclusions to be drawn.

An important rôle of medical management in this clinic is in connection with those cases which sooner or later are subjected to operation. Every patient entering hospital ward or clinic should have a thorough search for the existence of coincidental disease. The treatment of such associated conditions must often run parallel, or is interwoven with, the treatment of the thyroid dysfunction. An example of the importance of such coexistent disease is furnished by the following case:

Case I. Hyperthyroidism with Nephritis; Improvement Following Operation and Medical Treatment.—Fanny B., a colored woman aged thirty-seven, the mother of 3 children, was admitted to the service of Dr. Frazier on December 26, 1925, with a history of increasing nervousness, tremor, and insomnia ever since the death of a sister two years previously. There had also been progressive dyspnea, palpitation, and occasional edema of the ankles. She had become very weak, and had lost about 28 pounds since the onset of her symptoms. Slight exophthalmos had been observed, and her neck had shown a progressive enlargement during almost the whole period of her illness. Shortly before admission she had begun to have irregular attacks of nausea and vomiting, with severe orbital headaches. Occasional diarrhea had been present. Her previous history revealed an alleged attack of malaria many years before, influenzal pneumonia in 1918, and the removal of her right ovary and appendix in 1924. She had had 4 miscarriages, 2 of them spontaneous. She was born and raised in a non-goiterous district of Virginia and there was nothing of significance in her family history.

Examination showed a fairly well-nourished negro woman, very nervous and apprehensive, with a fine tremor of the hands, excessive sweating of the palms, and slight exophthalmos with lid-lag. There was a diffuse firm enlargement of the thyroid gland, much more marked in the right lateral lobe. There was no evidence of laryngeal dysfunction or of substernal extension of the goiter. The lungs showed nothing abnormal. There was slight cardiac enlargement both to right and left, with a systolic murmur heard over the base and the mitral area in the recumbent position. The blood-pressure on admission was 155/80, the pulse rate 108; there was no evidence of arteriosclerosis. Examination of the eye-grounds was negative. The abdomen showed an old laparotomy scar. Tendon reflexes were uniformly increased.

Blood-count showed 3,670,000 erythrocytes, 76 per cent. of hemoglobin, and 10,600 leukocytes. The blood Wassermann was negative. Phenolsulphonephthalein elimination was 23 per cent. in the first hour and 10 per cent. in the second (intravenous). The urine contained a cloud of albumin and many hyaline and epithelial casts on repeated examinations, and the specific gravity varied between 1.009 and 1.012. The blood urea nitrogen was 20 mgm. per 100 c.c. The basal metabolic rate was 40 per cent. above normal.

Our diagnosis was: (1) hyperplastic toxic (exophthalmic) goiter; (2) chronic diffuse nephritis; (3) secondary anemia. The thyroid dysfunction and the nephritis were thought to bear only a coincidental relationship to each other. It was thought advisable to observe the course of both her major diseases and at the same time to try to bring about improvement by rest, proper diet, and the careful use of iodin. Accordingly, she was transferred to the Medical Division, where she remained until February 21st, a period of seven weeks.

During this time her condition varied considerably, with a tendency toward improvement, although nausea and vomiting were troublesome at times. Her urine continued to contain albumin and casts, and showed a specific gravity never above 1.015. The blood-pressure remained elevated (at the end of four weeks it was 160/90) and the tachycardia persisted. The blood urea nitrogen rose to 35 mgm. soon after transfer, then fell to 16, and at the end of seven weeks was 20. The basal metabolic rate was 31.8 per cent. above normal after four weeks' rest. Her fluid intake varied between 1200 and 1800 c.c. daily, and the output between 680 and 1200 c.c. She was kept on a low protein, low salt diet, and received 0.3 c.c. (5 minims) of Lugol's solution three times daily during the last sixteen days of her stay in the medical ward.

Although the ultimate prognosis was considered poor because of her nephritis, it was thought that subtotal thyroidectomy offered the best chance for relieving the symptoms of thyrotoxicosis and assisting in the prolongation of life. Accordingly, she was transferred back to Dr. Frazier's service, and a subtotal thyroidectomy was performed under local anesthesia by Dr. Mosser, the surgical representative in the Thyroid Clinic, on February 27th. She stood the operation remarkably well and her convalescence was uneventful. She was kept under observation until March 14th; during this time the urinary findings remained the same as before operation and the blood urea nitrogen stayed at 23 mgm., but there was a drop in systolic blood-pressure to 136 (the diastolic remained at 90), the pulse rate came down to 80, and the basal metabolism was reduced to 9 per cent. above normal. Her weakness and nervousness were much less marked and she was discharged considerably improved.

She was seen again on April 1st; her weight was then 120 pounds. She felt much improved, with excellent appetite and no gastric symptoms, and complained of some dyspnea and palpitation only on severe exertion. There had been no recurrence of edema, the exophthalmos had receded slightly, and her nervousness and tremor were much reduced. Her pulse rate, however, was 100, the blood-pressure 168/100, and the 'phthalein

output in two hours (intravenous) was only 30 per cent. Urinalysis still showed a cloud of albumin and many casts, with a specific gravity of 1.010. The blood urea nitrogen was 18 mgm. per 100 c.c. and the basal metabolic rate 9 per cent. plus.

It will be seen that by co-operative medical and surgical management her symptoms have been considerably alleviated, her condition somewhat improved, and her life expectancy, which is probably not great at best, at least prolonged.

The preparation of patients with cardiac disease for operations on the thyroid gland is often a difficult task. Despite controversies as to the extent or frequency of actual myocardial lesions, the fact remains that many thyrotoxic patients exhibit evidence of progressive cardiac weakness, usually associated with tachycardia and arhythmias (chiefly auricular fibrillation and extrasystoles), and often leading to congestive heart failure or sudden cardiovascular collapse on the occurrence of the thyroid "crisis." Many patients with far advanced decompensation can, by persistent and judicious treatment, be prepared for operation and a satisfactory restoration of function secured. Complete rest is, of course, essential, and the use of digitalis and Lugol's solution is often important. There is occasionally a surprising tolerance to digitalis, and very large amounts may sometimes be given without evidence of therapeutic or toxic effect. Dr. Wolferth and the writer, in a review of 201 consecutive admissions of patients with thyroid disease to Dr. Frazier's service (to be published), found 18 cases with sufficient evidence of cardiac disease to warrant special medical treatment. All of these 18 patients were operated upon; 3 failed to survive, and 2 of these deaths were attributable directly to heart disease; 7 showed established auricular fibrillation, and 4 (including the fatal cases), paroxysmal fibrillation. We concluded from our study of these 18 cases that digitalis is of no apparent value in reducing the rate in thyrotoxic patients with normal rhythm, or in preventing the occurrence of paroxysmal fibrillation. When used with Lugol's solution, as is indicated in the true hyperplastic toxic (exophthalmic) cases a restoration of compensation can often be secured, which is impossible with the use of digitalis alone. Digitalis has a distinct

tendency to reduce the ventricular rate in established or paroxysmal fibrillation.

The following case history illustrates the good results that may be secured in treating cardiac incompetence before operation:

Case II.—Toxic Adenoma with Myocardial Failure; Tolerance to Digitalis; Improvement and Successful Operation.—Mrs. Minerva S., white, aged forty-eight, was admitted to Dr. Frazier's service May 4, 1923, complaining of a goiter, shortness of breath, and swelling of the legs. She had had a goiter twenty-two years before, which had disappeared coincidently with some kind of electric treatment. She had always been rather nervous. In August, 1922, while in the early stages of the menopause, enlargement of the right lobe of the thyroid was noted, with fatiguability, palpitation, and increasing nervousness. These symptoms had increased progressively up to the time of admission. Dyspnea and edema of the legs appeared in December, 1922, with an increase in the severity of the palpitation. In January she was forced to go to bed, where she remained for nine weeks, with disappearance of the edema; this, however, promptly reappeared on getting up again. She was unable to do any work, slept poorly, and had a chronic cough productive of bloody mucus. There had been loss of weight (amount unknown) and progressive weakness. Her previous medical history and family history contained nothing of importance.

On admission the patient appeared markedly dyspneic; there were numerous râles at the bases of both lungs, and signs of pleural effusion on both sides. The heart was enlarged greatly to the left, with a diffuse precordial impulse and a palpable thrill over the apex. There was a total arhythmia (auricular fibrillation) and a rapid ventricular rate (140). There was a considerable pulse deficit; the blood-pressure could not be accurately determined. Abdominal examination showed signs of hepatic enlargement and ascites, and there was marked edema of the lower back and both legs up to the knees. There was a firm nodular enlargement of the thyroid and definite exophthalmos, with lid-lag and widening of the palpebral fissure.

x-Ray of the chest showed effusion in both pleural cavities. The basal metabolic rate was 59 per cent. above normal three days after admission. Blood-count showed 4,510,000 erythrocytes, 88 per cent. hemoglobin, and 8600 leukocytes. The urine contained a cloud of albumin and a variety of casts for several days after admission, but these findings disappeared as the patient's condition improved. Phenolsulphonephthalein output was normal. A diagnosis of toxic adenoma of the thyroid, with myocardial disease, auricular fibrillation, and decompensation was made. The patient was seen in consultation by Dr. Wolferth, who recommended the administration of powdered digitalis, 0.06 gm. (1 grain) four times daily. She was, of course, kept absolutely at rest.

Improvement was somewhat slow in appearing; the ventricular rate did not decrease, and the edema persisted, although the

dyspnea was somewhat improved. On May 12th the ventricular rate was 140, although almost 2 grams (29 gr.) of digitalis had been given. There were no signs of digitalis intoxication, and on May 15th the dosage was changed to 0.13 gram (2 gr.) three times daily. Soon after this a striking improvement began, and by May 20th the ventricular rate had dropped to 80, the arhythmia consisted of extrasystoles alone, the liver enlargement, ascites, and peripheral edema had almost disappeared, and the patient was much more comfortable, with very little dyspnea. Her condition was considered satisfactory for operation, and on May 23d, under local anesthesia, the adenomatous mass was removed by Dr. Frazier. There was postoperative bleeding, which necessitated reopening of the wound, and this resulted in a secondary infection. She stood the operation and subsequent procedures very well, and with continuation of digitalis, on May 24th, her heart action was perfectly regular with a rate of 92. Pulsus bigeminus was noted at that time, and the digitalis was stopped. She left the hospital June 17th with a regular rhythm, a pulse rate of 82, and no evidence of cardiac incompetence. During her stay she received a total of 86 grains (almost 6 grams) of powdered digitalis, and exhibited only pulsus bigeminus as evidence of toxic effects. Because of the nature of her thyroid disease (toxic adenoma) iodin was not given, as it has not been shown to be of value in these cases.

The commonest postoperative conditions demanding medical care in our experience have been cardiac irregularities with or without evidence of insufficiency, respiratory infections, and acute thyrotoxic crises, often associated with cardiovascular breakdown. Time does not permit the discussion of these conditions other than to note the frequency of tracheobronchitis following all types of operation on the thyroid, and to mention that the crises are of grave significance, require heroic measures, and often end fatally. The continuation of Lugol's solution after operation in the true hyperplastic toxic (exophthalmic) goiters is of importance in preventing the occurrence of these crises; blood transfusion, ice-packs for hyperthermia, copious

administration of fluids, sedatives, and digitalis are other therapeutic weapons.

Despite the large literature, and the vast number of patients with hyperthyroidism who have come under observation, the amount of accurate information as to the final results following various forms of treatment is far too scant. It is of the greatest importance that we know what becomes of our patients with Graves' disease or toxic adenoma not only months, but years after treatment; the progress of cardiac lesions, the recurrence of the nervous symptoms, the level of basal metabolism, changes in body weight, restoration of economic usefulness—all of these should be known. It is only by careful dispassionate study of such information, accurately and painstakingly gathered, that the various types of treatment can be compared, and the value of each, with the indications for its use, can be determined.

Summary.—Although there is still some difference of opinion, subtotal thyroidectomy is generally considered the treatment of choice in most cases of true hyperplastic toxic (exophthalmic) goiter and of so-called toxic adenomata of the thyroid.

Medical supervision is essential in order that the best results may be secured from surgical treatment, and close co-operation between internist and surgeon greatly improves the patient's chances for relief.

The detection and treatment of coexistent disease, including cardiovascular complications and the management of thyrotoxic crises, constitute important phases of medical supervision.

Prolonged observation of patients after discharge from hospital, in order to determine functional end-results, is of vital importance in any attempt at evaluation of various forms of therapy.

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TUBERCULOUS PERICARDITIS WITH TUBERCULOSIS OF THE MYOCARDIUM AND ENDOCARDIUM

THE first reported case of tuberculous pericarditis was by Corvisart.[1] Some years later 2 other cases were reported by his famous pupil, René Theophile Hyacinthe Laennec. In view of the fact that the present year marks a century since the death of Laennec, it is fitting to recall that Laennec died on August 13, 1826, in Brittany, the land of his birth. Although he lived only to the age of forty-five, yet his discovery of mediate auscultation and his subsequent observations removed the subject of the diagnosis of chest diseases from the realm of philosophic speculation, and for the first time placed it on a rational basis. In 1816 he discovered the stethoscope, and only three years later he published the epoch-making work, "De l'Auscultation Médiate." In the first edition he mentioned the case of tuberculous pericarditis reported by Corvisart,[2] and in the second edition, published in the year of his death, he described having seen 2 cases himself.[3]

The statistics relative to the incidence of tuberculous pericarditis at necropsy have been estimated by various methods. In 1000 autopsies Osler[4] reported 275 tuberculous subjects, of which 7 had tuberculous lesions of the pericardium. In an examination of 7219 protocols Norris[5] reported 1780 tuberculous subjects, in which tuberculous pericarditis was present in 82. In these 82 cases 32 contained tubercles. In the other cases there was no distinctively tuberculous pathology in the pericardium, but all other diseases causing pericarditis had been excluded. Tuberculosis may produce simply a fibroplastic process in which

the adhesions and the pericardial membranes contain no evidence of tuberculosis. Wells,[6] in a series of 1048 necropsies, reported tubercles or caseation in the pericardium in 10 cases. Brooks and Lippencott,[7] in the examination of 1000 protocols, reported 6 cases of frankly tuberculous pericarditis, and 17 cases of chronic adhesive pericarditis without tubercles or caseation, but in which tuberculosis was the etiologic factor. It would appear, therefore, that at necropsy in patients dying of all causes the incidence of tuberculous pericarditis with definitely tuberculous lesions is about 0.5 per cent. The incidence of chronic adhesive pericarditis due to tuberculosis, but without distinctive pathology, is much higher. It is generally agreed that, next to rheumatic fever, tuberculosis is the most common cause of chronic adhesive pericarditis, but not of acute pericarditis.

While tuberculous pericarditis is a fairly frequent disease, the vast majority of cases are secondary to a tuberculous process somewhere else in the body, and there have been reported only a very few cases in which other tuberculous lesions could not be demonstrated. Hedbloom[8] collected 13 cases of primary tuberculous pericarditis in the literature and reported a case himself, and Rawls[9] has recently reported another case. Most authors agree that tuberculous pericarditis is usually due to a direct extension from caseous mediastinal glands. Landis,[10] however, doubts this because of the relative infrequency of the disease in association with chronic pulmonary tuberculosis, and believes that infection by the blood-stream seems the most probable because of this mode of transmission in other viscera. It seldom happens that caseous glands rupture their capsule and discharge their contents directly into the pericardial sac. Metcalf[11] states that the ordinary mode of infection is through the lymph-stream, from caseous mediastinal glands, the bronchial glands in particular, though this necessitates a reversal of the direction of flow of the lymph. In some cases the infection takes place by direct extension from the pleura.

The pathologic appearances vary greatly. In general the acute form is marked by exudation—fibrinous, serofibrinous, hemorrhagic, or purulent—while the chronic form is characterized

by thickening of the membranes, tubercles, caseation, and adhesions in various proportions. The amount of exudate may be very large, amounts up to 4000 c.c. having been reported. The chronic form is the more common. In the chronic adhesive form there is hypertrophy of the myocardium, which may be very marked. There are more or less fatty and fibroid changes, but cases in which the myocardium is deeply infiltrated (1 cm. or more) by the tuberculous process are of moderate rarity, the auricles being more often infiltrated than the ventricles. Norris, in his series of 82 cases of tuberculous pericarditis, reported the myocardium to be infiltrated in 5.

Clinically, cases of tuberculous pericarditis may be divided into those which present cardiac symptoms, either of acute pericarditis or of cardiac failure due to chronic adhesive pericarditis, and into those which do not present cardiac symptoms. The latter may have the symptoms of a general acute tuberculous infection, or they not infrequently may have no symptoms at all, and the pericardial disease may be discovered only accidentally at necropsy after the subjects have died of other causes.

The diagnosis of acute pericarditis with effusion is usually not difficult, but is often overlooked. If the commoner causes, such as rheumatic fever, pneumonia, sepsis, and nephritis, can be excluded, and if an active tuberculous focus is known to exist, the evidence is presumptive that the pericarditis is tuberculous. A hemorrhagic exudate is added evidence that the process is tuberculous. A positive guinea-pig inoculation may clinch the diagnosis. Chronic adhesive pericarditis is usually a difficult diagnosis to make. The most reliable physical signs are absolute or abnormal immobility of the heart, with change of posture from right to left, a systolic retraction of the interspaces at the apex and posteriorly on the left side between the eleventh and twelfth ribs (Broadbent's sign), and the presence of a diastolic shock, but adherent pericardium should be suspected in any case in which the heart is enlarged, and in which the functional capacity and failure to respond to treatment seem to be out of proportion to a discoverable cause. If the other common causes of pericarditis can be ruled out, if the endocardium seems to be

normal, and if a tuberculous lesion can be found elsewhere, we may strongly suspect tuberculosis as the etiologic factor.

Case Report.—J. S., a male negro, nineteen years of age, entered the Pennsylvania Hospital, on the service of Dr. George W. Norris, June 18, 1925. His occupation was given as an actor, a dancer. His chief complaint was pain in the back.

His family history and his past history were negative. He said he had never been sick. He had never had rheumatic fever, chorea, or tonsillitis. He denied venereal infections.

History of Present Illness.—For eight or nine months he had had vague twinges in his back. For three weeks prior to admission the pain had been severe. It was described as a severe ache, rather diffuse, but maximum along the posterior portion of the right iliac crest. At times it was absent. It seemed to be worse when he was lying down. He had had no dyspnea, palpitation, or edema. He gave a vague history of having had some precordial pain, but he had had none recently. He had had a cough for about a month, with abundant expectoration, but with no hemoptysis nor pain in the chest. For the past six months he had had night-sweats. His best weight had been 130 pounds two years previously and on admission was 100.

Physical Examination.—The patient was of a frail build and was somewhat undernourished. He did not appear to be acutely ill. There was no dyspnea or cyanosis. His eyes, ears, nose, tonsils, and teeth appeared to be healthy. His tongue was not coated and his breath was not foul. There was no adenopathy. There was slight restriction of expansion of the left upper chest. There was no impairment of resonance, no abnormality of breath sounds or of whispered voice sounds, and no râles. The heart had a very overactive apex impulse, diffuse in the third, fourth, and fifth interspaces. There was a slight systolic heave. The right border was 4 cm. to the right of the midsternal line in the fourth interspace, and the left border was $12\frac{1}{2}$ cm. to the left in the fifth interspace. The rhythm was regular and the rate was 96. The sounds were distant and muffled. There was a short, high-pitched, systolic murmur at the apex with the patient lying on his left side. The cardiac dulness shifted on changing the patient's position. There was gallop rhythm at the apex. There was no Broadbent's sign. His blood-pressure was 110/74. The liver extended 2 cm. below the costal margin in the midclavicular line. The abdomen was otherwise normal. There was no evidence of disease of the spine. There was no edema of the legs and no clubbing of the fingers.

The average daily range of his temperature was 99° to 101° F.; of his pulse, 90 to 110; of his respirations, 24 to 30.

His urine, sputum, blood-culture, and Wassermann examinations were all negative. His blood showed Hb. 90 per cent., R. B. C. 4,700,000, and W. B. C. 10,600. The *x*-ray examination showed no evidence of pathology of the lumbar spine or sacro-iliac region. There was no definite evidence of lung pathology, although there was some peribronchial thickening on both sides. The heart seemed to be greatly enlarged and the aorta appeared to be diffusely dilated. The outline of the arch could not be seen.

On one day his heart showed auricular fibrillation, as proved by the electrocardiogram.

By July 1, 1925 the pain which brought him to the hospital had practically disappeared. He insisted upon leaving the hospital against advice. The discharge diagnoses were cardiac enlargement (due probably to tuberculous adhesive pericarditis), auricular fibrillation (transient), and dilation of the aorta.

Second Admission.—On October 8, 1925 he returned to the hospital. After leaving the hospital on July 1st he spent eight weeks in bed. Then he went to Atlantic City, where he went in swimming and "caught cold." Following this he went South for a month, returning to Philadelphia two days before admission.

His chief complaint at this time was dyspnea, which had begun about two months previously. Swelling of the abdomen and feet had been noted some time afterward and had steadily become worse. The pain, which was his chief symptom on the first admission, was not particularly complained of.

The patient was lying propped up in bed. He was moderately dyspneic and very toxic, but complained of no pain. His chest expansion was poor. At both bases there was definite dulness, with diminished breath sounds, and numerous inspiratory crackling râles. Over the right hilus bronchovesicular breathing was heard. The heart showed no precordial bulging or heave. There were no systolic retractions of the interspaces or a diastolic shock. The right border was 4.5 cm. to the right of the midsternal line in the fourth interspace and 12 cm. to the left in the fifth. The sounds were muffled and the first sound at the apex terminated in a faint systolic murmur. The abdomen was distended with fluid and the liver extended downward almost to the level of the umbilicus. There was only slight edema of the ankles.

The urine examinations were negative except for traces of albumin. W. B. C. 13,000. Four sputum examinations were negative for tubercle bacilli. The Wassermann and blood-culture were negative, and the electrocardiogram was normal.

The *x*-ray examination of his chest showed a very finely mottled shadow over the entire lung area. In view of the fact that this was not present four months previously, it could only be due to miliary tuberculosis. The heart was greatly enlarged. The first lumbar vertebra (on the edge of the film) showed some destruction.

His temperature was very hectic in character and ranged for the most part between 98° and 103° F. The pulse rate was very rapid, averaging 140, and his respirations were 30 to 48.

On October 11th his abdomen was tapped and 800 c.c. of clear greenish-yellow fluid obtained. On October 19th a swelling was noted for the first time to the right of the ninth dorsal vertebra, which was considered to be a cold abscess. On October 21st the eye-grounds showed no lesions. On November 3d the patient died. The clinical diagnoses were chronic adhesive tuberculous pericarditis, tuberculosis of the first lumbar vertebra, and miliary tuberculosis.

The findings at necropsy, performed by Dr. J. T. Bauer, chiefly concerned the thoracic cavity. There were a few pleural adhesions scattered over the

right lung, but no free fluid in either pleural cavity. The pericardium was densely adherent to the pleura, but not to the thoracic wall. The pericardial layers were firmly adherent, completely obliterating the sac. The pericardium was markedly thickened and studded with tubercles. Yellow areas extended into the myocardium, both of the auricles and ventricles, to a depth of 10 mm., with considerable destruction of the muscle. In the auricles these areas extended through to the endocardium, so that the endocardium was covered with numerous small patches. The valves were apparently com-

Fig. 33.—Extensive tuberculous infiltration of the myocardium in the auricles involving the endocardium.

petent. The heart weighed 490 grams. The lungs were studded with miliary tubercles, uniformly scattered, 1 to 1.5 mm. in diameter. Careful search was made for focal pulmonary tuberculosis, but none was found. The lymph-nodes at the hilum of the lungs contained a few small gray nodules. At the root of the left lung the cellular tissue about the vessels and outside the lymph-nodes was indurated and contained patches of caseation 1 to 6 mm. across. This indurated tissue was continuous with similar indurated tissue, much more extensive, in the mediastinum on both sides of the trachea and

intimately adherent to the adjacent large vessels. This tissue was gray, indurated, much thickened, and flecked with spots of caseation. The peritoneum, liver, kidneys, and spleen contained miliary tubercles. The mesenteric glands were enlarged and contained patches of caseation. There was a general disintegration of the first lumbar vertebra, and slight extension of the process to the twelfth thoracic and second lumbar vertebræ, with an abscess cavity extending along the right side of the spine and dissecting the tissues to within a few millimeters of the skin.

Discussion.—At the time of the first admission the outstanding fact was a heart much enlarged without any apparent cause. There was no history of the rheumatic triad. Save for a short systolic murmur, there was nothing to indicate involvement of the endocardium. There was no evidence of syphilis, and arteriosclerosis in a youth of nineteen could hardly be considered. By the process of elimination adherent pericardium seemed the most probable cause of the cardiac enlargement, with tuberculosis as the etiologic factor. Although no focal tuberculosis could be found, its presence was strongly suspected because of fever, cough, night-sweats and loss of weight, the negative blood-cultures, and absence of leukocytosis. At the second admission the presence of tuberculosis in the lungs and spine was evident, and the diagnosis of tuberculous pericarditis could be made then with considerable confidence. At the time of his first admission, in spite of the fact that disease of the heart had existed for a sufficient period to produce marked enlargement, his cardiac function was not seriously impaired. Probably at this time he would not have sought medical advice if it had not been for the pain in his back, the cause for which was not found then, but which undoubtedly was due to beginning involvement of the vertebræ.

It would seem that the tuberculosis had its origin in the peribronchial lymph-glands, whence it spread to the mediastinum, pericardium, and spine in the order named. It is probable that after the tuberculous process had extended through the myocardium to the endocardium the disease became miliary, with the endocardium as the focus of dissemination. From a pathologic point of view the case is very unusual because of the extensive tuberculous involvement of the myocardium.

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